Topical Insulin and Fractional Laser in Management of Acne Scars: Review Article

Amin Mohamed Amer, Al-Shimaa Al-Tohamy Goda*, Fathia Mohamed Khattab
Department of Dermatology, Venereology & Andrology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Al-Shimaa Al-Tohamy Goda, **Mobile:** (+20) 01151462960, **E-Mail:** shimaatohamey@gmail.com

ABSTRACT

Background: Eighty percent or more of teenagers will experience acne. The acne scars left behind by acne vulgaris are irreversible. Up to 95% of people with acne vulgaris may experience scarring, yet this issue has received little attention from researchers. Depending on the study, acne scars affect between 1% and 11% of the population. Lasers have great potential as a therapeutic tool, but it has been difficult to get desirable clinical results because of the inherent trade-off between efficiency and safety, especially with the first generation of ablative lasers. Current research suggests that topical insulin may be effective in reducing the appearance of acne scars. Increased VEGF is produced after topical insulin activates PI3K/AKT pathways. Unlike the crisscross pattern typical of scar tissue, the collagen fibres generated and developed in normal skin more closely resemble a "basket weave. ".

Objective: Assessment of possible role of topical insulin and fractional laser in the treatment of acne scars.

Methods: PubMed, Google Scholar, and Science Direct were scoured for information about: Acne scars, fractional laser therapy and topical insulin. The authors also reviewed additional sources, but only the most up-to-date or comprehensive study between April 2004 and April 2021 was included. There are no translation resources available, thus non-English documents are out. Dissertations, conference papers, and oral presentations were not included since they do not constitute "important scientific discoveries."

Conclusion: It's possible that post-acne scars can be effectively treated with either topical insulin or fractional laser. Larger controlled studies are needed to confirm the effectiveness of insulin as a novel anti-scarring medication.

Keywords: Topical insulin, Fractional laser, Acne scars.

INTRODUCTION

To a greater or lesser extent, up to 80% of the adolescent population suffers from acne. Scarring that doesn't fade with time is an undesirable side effect of acne vulgaris. Although acne scarring has not been thoroughly investigated, it may affect up to 95% of patients with acne vulgaris. Scarring from acne appears to affect between 1% and 11% of the population, according to studies[1-3]**.** The emotional and psychological toll of acne scarring can be significant. Like acne, acne scars are linked to low self-esteem, sadness, anxiety, impaired social interactions, altered body image, shame, rage, poor academic achievement, and unemployment. Scars don't typically fade with time and, due to ageing or sun damage, may even stand out more [2]**.** There are three basic types of acne scars: Atrophic, hypertrophic, and keloidal. Atrophic acne scars are the most common kind. Though inflammatory mediators, enzymes that tear down collagen fibres and subcutaneous fat, and genetics all play a role, the exact origins of atrophic acne scars remain unknown [3]**.**

Eighty percent of teenagers have acne, with 10 to 20% having severe cases. According to 1996 study, acne affects between 40 and 50 million Americans, with a peak incidence (85%) among those aged 12 to 24 [4]**.**

Insulin is an endogenous peptide and growth factor that has multiple functions in the body. Past research has established the existence of insulin receptors in the epidermis' keratinocytes and fibroblasts, so the topic of insulin's function in the skin is not new. Increasing numbers of human keratinocytes require insulin**.** Moreover, insulin can recruit healing-related cells and stimulate their proliferation. Insulin has been demonstrated to have a significant role in the creation of granulation tissue by boosting protein synthesis in the skin and encouraging the growth and development of various cell types, including keratinocytes, endothelial cells, and fibroblasts [5]**.**

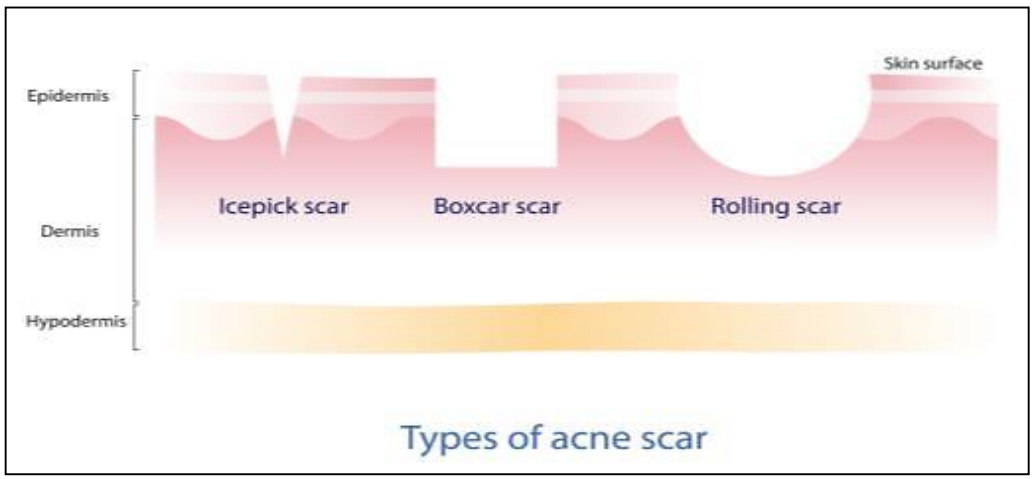

Figure (1): Acne scar classification [5]

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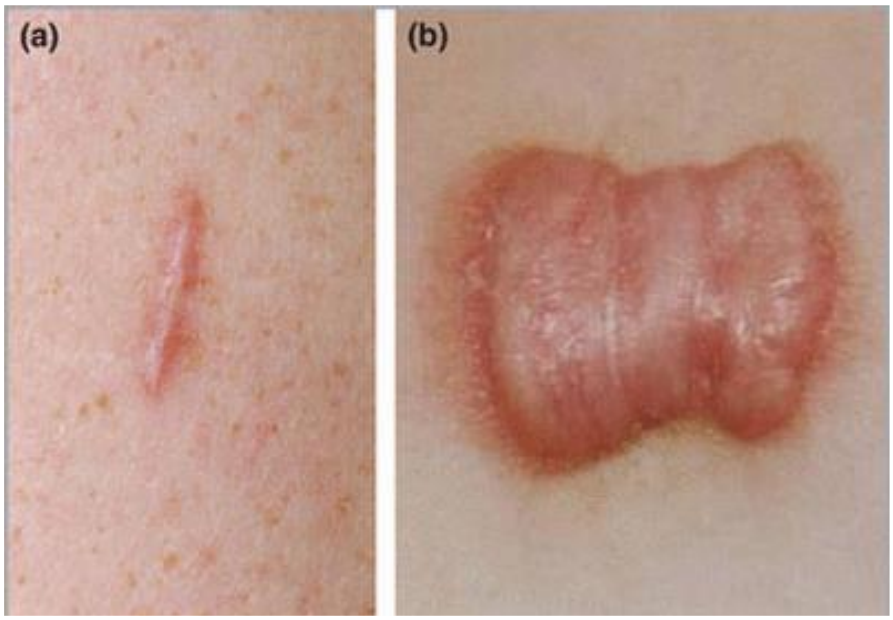

Figure (2): (a) Hypertrophic and (b) Keloid Scars [5]

Topical Insulin and Fractional Laser in Acne Scars:

Light/lasers and radiofrequency, two energy-based technologies, have recently emerged as a promising noninvasive option among the many treatments available for acne scars. The elimination of pigment and erythema, as well as the creation of collagen and elastin, all depend on the wavelength of the light received by chromophores in the epidermis and dermis **(6)**.

Although lasers have therapeutic promise, achieving ideal clinical outcomes has proven difficult due to the fact that efficacy is typically exacerbated by adverse effects. This is especially true with the earlier generation of ablative lasers. In contrast, nonablative lasers are safer to use but produce less spectacular therapeutic outcomes **(7).** Since the 1970s, researchers have examined the effects of topical insulin on wound recovery. Topical Insulin treatment has been shown to work via the IGF-1 receptor in a number of animal models and human investigations. There was a significant increase in epithelization rates in diabetic foot patients who used topical insulin. Evidence suggests that insulin promotes neovascularization and granulation tissue development by increasing keratinocyte and endothelial proliferation **(8).**

Ablative non-fractional lasers:

Although ablative lasers can cause significant dermal remodeling, they come with unpleasant side effects such as prolonged redness, swelling, bleeding, and crusting that must be dealt with during the recovery period **(9).**

The epidermal layer of skin is removed during ablative laser treatments by superheating the water molecules there and vaporising them. Thermal injury below the vaporisation zone stimulates dermal cells to create additional collagen, which significantly improves photodamaged skin, scars, dyschromias as well as rhytides **(10).**

In contrast to haemoglobin and melanin, the wavelength at which water in tissues absorbs CO_2 laser light is different. It is possible to achieve optical depths of 20-30 mm with pulse durations < 1 ms and fluences of 5 J/cm^2. Since the wavelength of erbium-doped yttrium aluminium garnet (Er:YAG) lasers is only 2940 nm and their penetration depth is just 1-3 mm, these lasers are less obtrusive than CO_2 lasers when used for resurfacing **(11).**

One of the most common and potentially harmful adverse effects of ablative nonfractional lasers is reactive hypermelanosis of the skin, also known as post inflammatory hyperpigmentation (PIH). Macules or patches that don't cause any symptoms are typical of PIH. Due to an increased risk of photosensitivity responses, patients with darker skin tones should have a patch skin test before undergoing laser treatment) **(12).**

One way to lessen the impact of these side effects is to treat lesions with fewer passes, utilise lower fluences, and employ pulsed lasers rather than scanning ones **(6).**

Ablative fractional lasers:

The development of ablative fractional lasers in line with fractional photothermolysis, were created as a solution to the lengthy recovery time and related negative consequences of ablative lasers. Microthermal treatment zones (MTZ) are small columnar areas of thermal injury that are applied to the dermis to promote collagen growth **(13).**

For acne scars, the Er:YAG laser platform may be toggled to integrate fractionated technology, making it a fractional ablative laser device on par with the CO_2 laser in terms of popularity. Patients nevertheless occasionally have unfavourable side effects such erythema, edoema, scarring, and pigment irregularities, despite the fact that the newest generation of fractional lasers is more successful than their nonfractional predecessors. Although there is no way to completely eliminate the risk of side effects, many authors maintain

that they can be lessened by tailoring treatment parameters to each patient's skin type and by properly following the manufacturer's recommendations [14].

However, when both options are available, non-ablative fractional laser resurfacing is preferred because of its lower risk of complications and similar efficacy to ablative fractional lasers [15].

Non-ablative lasers:

Non-ablative laser technology has also been shown to be effective in treating atrophic acne scars. Type I and III collagen and elastic fibres are stimulated by the visible and infrared (IR) light from these sources. Because the epidermis is spared in the process, patients have fewer negative effects and have less downtime with non-ablative lasers. It may take multiple therapy sessions to see some clinical improvement in patients with icepick and boxcar scars [6].

The epidermis is shielded from the laser's rays and the upper papillary dermis is stimulated to produce collagen, however the patient is typically provided with cooling technology to alleviate any discomfort they may experience. Some non-ablative lasers are used to remove pigment and erythema in atrophic scars, in addition to matrix remodeling. Because discoloration draws attention to acne scars, reducing erythema and pigmentation is a crucial and frequently initial step in acne scar treatment [16].

Several different types of nonablative lasers exist for treating acne scars, including 1450 nm diode lasers, 755 nm alexandrite picosecond lasers, 58 and 595 nm pulsed-dye lasers, and erbium:YAG lasers. The 755 nm laser is often used to treat pigment, whereas the PDL laser is used to treat erythema. PDL treatment decreases scar erythema by focusing on oxyhemoglobin inside the skin's vascular systems. In many cases, the best outcomes can only be achieved after three or four treatments, each spaced roughly a month apart [17].

Non-ablative fractional lasers:

In 2003, non-ablative fractional lasers were introduced to the market with the intention of enhancing the efficacy of scar treatment while decreasing the downtime and adverse effects associated with it [17].

Water in the dermis is the primary target of the 1550 nm Er:Doped laser, which causes controlled thermal damage by gradually heating the water there. The fractionated laser feature preserves the epidermis's ability to mend by injuring it in a controlled, uniform way across the treatment region. You can also get 1540 nm and 1540/1550 nm combo lasers in this frequency range. Er:glass/1927 thulium fibre laser can be used for both ablative and non-ablative procedures [17].

Using the combined apex pulse approach, the 1440 nm fractionated laser can penetrate the skin to a depth of 300 mm and deliver energy in pulses to cure acne scars. Non-ablative fractional lasers leave the epidermis unharmed, reducing the risk of complications like erythema, edoema, haemorrhage, crusting, infection, and scarring**.** These lasers are effective on patients of all skin tones, however there is a larger risk of hyperpigmentation in individuals with darker skin. Non-ablative fractional laser resurfacing typically entails a series of four to six sessions, each separated by one month [18].

Topical insulin:

Topical insulin for decubitus ulcers was tested in a small pilot research. Eight control participants got just standard supportive nursing care, while six experimental individuals received usual supportive nursing care with regular insulin (10 U twice daily) for 5 days. By day 15, there was a statistically significant difference in the rate of wound healing between the treatment and control groups, and there had been no hypoglycemia or other adverse effects. The findings supported the hypothesis that insulin is a viable treatment option for minor, uncomplicated decubitus ulcers [19].

In **Rezvani *et al.*** [20] study, topical insulin was tested in a randomised, double-blind, placebo-controlled study including 45 persons with noninfected acute and chronic limb wounds. Volunteers were randomly assigned to receive either a saline solution spray twice daily or a crystalline insulin spray (10 U) twice daily. The treated group healed at a rate of 46.09 mm^2/day, while the control group healed at a rate of 32.24 mm^2/day ($P = 0.029$). No hypoglycemic symptoms were reported in either treatment group after insulin was given. There were no incidences of wound infection or uncontrolled bleeding, and no patients complained of any local pain during therapy. Insulin dosing and formulation variations may account for the conflicting results.

Several studies have looked into how topical insulin helps diabetic wounds recover. A randomised, double-blind, placebo-controlled experiment was conducted with 22 patients to determine the efficacy of topical insulin in treating diabetic wounds. Insulin cream (n=11) or placebo cream (n=11) was applied to half of the subjects twice daily for eight weeks. At week 8, the wounds of the 10 patients who had been given insulin cream had improved much more than those of the placebo group [21].

The effectiveness of local insulin injection was studied by **Martinez *et al.*** [22] in a group of eight diabetes patients with both acute and chronic wounds. Each time, insulin (10 U) was applied once daily for 14 days to half of the incision area while the other half was left untreated. The insulin group had higher mean temperatures, fibrosis percentages, and total vessel counts than the placebo group. Five years later, Martinez's team ran a second experiment on the same 10 patients who had sustained full-thickness acute wounds. New vascular growth rates in the insulin-treated areas were significantly different from those in the saline-treated portions, but the fibrosis % was unaffected.

In addition, **Zhang *et al.*** [23] revealed that researchers examined the effects of intralesional insulin

on blood sugar and wound healing in patients with diabetic foot ulcers. In the experimental group (n=18), insulin was injected directly into the base of the ulcer twice daily for 7 days, while in the control group (n=14), insulin was administered subcutaneously into the belly. Both the insulin and control groups had equal fasting blood sugar levels, however the insulin group had superior granulation tissue and new vessel creation.

Currently, a novel therapy approach for acne scars is being developed, and it involves the use of topical insulin [(24)]. After topical insulin is applied, the PI3K/AKT pathways are activated, leading to a rise in vascular endothelial growth factor (VEGF). As a result, more type III collagen is produced and matured, and these fibres organize themselves in a basket weave pattern, as in normal skin, as opposed to the crossing pattern seen in scar tissue [(25)].

CONCLUSION

It's possible that post-acne scars respond as well to both topical insulin and Fractional Laser treatment. Larger controlled studies are needed to confirm the effectiveness of insulin as a novel anti-scarring medication.

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REFERENCES

1. **Lynn D, Umari T, Dunnick C *et al.* (2016):** The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther., 7: 13-25.
2. **Ngaage M, Agius M (2018):** The psychology of scars: a mini review. Psychiatria Danubina, 30: 633-638.
3. **Lee Y, Lee C, Shin M (2021):** A neglected acne scar type: papular acne scars and their correlations with keloid scars. Dermatologic Surgery, 47: 1347-1351.
4. **Bernales S (2021):** Acne vulgaris: role of the immune system. International Journal of Dermatology, 60: 1076-1081.
5. **Quitério M, Simões S, Ascenso A *et al.* (2021):** Development of a topical insulin polymeric nanoformulation for skin burn regeneration: an experimental approach. Int J Mol Sci., 22 (8): 4087. doi: 10.3390/ijms22084087.
6. **Sadick N, Cardona A (2018):** Laser treatment for facial acne scars: a review. Journal of Cosmetic and Laser Therapy, 20: 424-435.
7. **Lanoue J, Goldenberg G (2015):** Acne scarring: a review of cosmetic therapies. Cutis, 95: 276-81.
8. **Lioutas V, Alfaro-Martinez F, Bedoya F *et al.* (2015):** Intranasal insulin and insulin-like growth factor 1 as neuroprotectants in acute ischemic stroke. Translational Stroke Research, 6: 264-275.
9. **Majid I, Imran S (2014):** Fractional CO_2 laser resurfacing as monotherapy in the treatment of atrophic facial acne scars. Journal of Cutaneous and Aesthetic Surgery, 7: 87-92.
10. **Oram Y, Akkaya A (2014):** Refractory postinflammatory hyperpigmentation treated fractional CO2 laser. The Journal of Clinical and Aesthetic Dermatology, 7: 42-44.
11. **Lee S, Kang J, Chung W *et al.* (2014):** Ablative non-fractional lasers for atrophic facial acne scars: a new modality of erbium: YAG laser resurfacing in Asians. Lasers in Medical Science, 29: 615-619.
12. **Woo S, Park J, Kye Y (2004):** Resurfacing of different types of facial acne scar with short-pulsed, variable-pulsed, and dual-mode Er: YAG laser. Dermatologic Surgery, 30: 488-493.
13. **Bencini P, Tourlaki A, Galimberti M *et al.* (2012):** Nonablative fractional photothermolysis for acne scars: clinical and in vivo microscopic documentation of treatment efficacy. Dermatologic Therapy, 25: 463-467.
14. **Cho S, Lee S, Cho S *et al.* (2010):** Non-ablative 1550-nm erbium-glass and ablative 10 600-nm carbon dioxide fractional lasers for acne scars: a randomized split-face study with blinded response evaluation. Journal of the European Academy of Dermatology and Venereology, 24: 921-925.
15. **Ong M, Bashir S (2012):** Fractional laser resurfacing for acne scars: a review. British Journal of Dermatology, 166: 1160-1169.
16. **Kwok T, Rao J (2012):** Laser management of acne scarring. Image. Skin Therapy Lett., 17 (2): 4-6.
17. **Badawi A, Tome M, Atteya A *et al.* (2011):** Retrospective analysis of non-ablative scar treatment in dark skin types using the sub-millisecond Nd: YAG 1,064 nm Laser. Lasers in Surgery and Medicine, 43: 130-136.
18. **Zaleski-Larsen L, Fabi S, Mcgraw T *et al.* (2016):** Acne scar treatment: a multimodality approach tailored to scar type. Dermatologic Surgery, 42: 139-149.
19. **Wang J, Xu J (2020):** Effects of topical insulin on wound healing: a review of animal and human evidence. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 13: 719-27.
20. **Rezvani O, Shabbak E, Aslani A *et al.* (2009):** A randomized, double-blind, placebo-controlled trial to determine the effects of topical insulin on wound healing. Ostomy/Wound Management, 55: 22-28.
21. **Lima M, Caricilli A, De Abreu L *et al.* (2012):** Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. PloS One, 7: e36974. doi: 10.1371/journal.pone.0036974.
22. **Martínez-Jiménez M, Aguilar-García J, Valdés-Rodríguez R *et al.* (2013):** Local use of insulin in wounds of diabetic patients: higher temperature, fibrosis, and angiogenesis. Plastic and Reconstructive Surgery, 132: 1015-1019.
23. **Zhang Z, Lv L (2016):** Effect of local insulin injection on wound vascularization in patients with diabetic foot ulcer. Experimental and Therapeutic Medicine, 11: 397-402.
24. **Pawar M, Singh M (2020):** Microneedling with autologous platelet-rich plasma verses microneedling with topical insulin in the treatment of post-acne atrophic scars: a simultaneous split-face comparative study. J Am Acad Dermatol., 84: 810-11.
25. **Azevedo F, Pessoa A, Moreira G *et al.* (2016):** Effect of Topical Insulin on Second-Degree Burns in Diabetic Rats. Biol Res Nurs., 18 (2): 181-192.