

Role of Insulin in Dermatology: Review Article

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ABSTRACT

Background: Insulin exerts metabolic and growth-stimulating actions both through its own receptors and the receptors of its homologous factors (IGFs), although with different degrees of affinity. The A receptor of insulin acts more intensely on the cell membrane, with a metabolic response, whereas the B receptor is quickly internalized, stimulates cell growth, can be directed to the treatment of wounds difficult to heal. The intraregional use of insulin ensures its absorption, greater stability, longer activity period and absence of contact with necrotic or enzymatic materials capable of preventing or changes its activity in topical use.

Objective: in this article, we aimed to study the role of insulin in dermatology and skin diseases.

Methods: We searched online databases (PubMed, Embase, and the Cochrane Library), to include studies that discuss the role of insulin in skin diseases, all types of studies are included.

Conclusion: Insulin therapy has been shown to be effective and without adverse effects. Different intervals between applications did not change the obtained results. The availability of insulin and the safety of its use indicate the authors' method as an advantageous therapeutic option in the recovery of tissues. The availability, low cost and wide knowledge available on this substance justify its indication as a therapeutic method for, are difficult to heal wounds.

Keywords: Insulin, Growth factor, Wounds and injuries, Difficult wound healing, Insulin therapy, Lichen planus, Oral lesion.

INTRODUCTION

Insulin is peptide hormone released by pancreatic islets of Langerhans cells that preserves normal blood glucose levels by easing cellular glucose uptake, regulating carbohydrate, lipid, and protein metabolism, and promoting cell division & growth via mitogenic impacts ⁽¹⁾. In 1921, Insulin was eventually isolated, purified, & became available therapeutically in effective way. Since Banting's discovery of insulin many benefits other than regulating blood glucose have been documented ⁽²⁾.

The effect of insulin on wound healing has been reported in various animal wound models, containing fracture wounds, skin ulcers and incision wounds ⁽³⁾. In real, systemic insulin cure decreases infections following surgical procedures in diabetic studied cases & enhances pressure ulcer healing ⁽⁴⁾. This cure, even so, has disadvantage of causing hypoglycemia & hypokalemia. In diabetic and non-diabetic studied cases, however, topical insulin enhances wound healing without affecting blood glucose levels ⁽⁵⁾. Earlier research found that insulin could decrease inflammation & rise collagen deposition, resulting in faster burn wound healing. Furthermore, intralesional injected insulin that disperses into wound can hasten wound re-epithelialization ⁽⁶⁾.

Biology of wound healing

Hemostasis, inflammation, proliferation, & remodeling are all overlapping phases of wound healing. Hemostasis is 1st stage of healing after injury ⁽⁷⁾. Raised capillary permeability & cell migration to wound tissue characterize inflammation process. Neutrophils are 1st cells to infiltrate injured tissue & reveal proteases to minimize denatured extracellular matrix ⁽⁸⁾. Following that, since monocytes enter wound site, they are changed into macrophages by monocyte

chemotactic protein-1, growth factor- β , & other cytokines. These cells are involved in inflammatory response & in resolution of fibrin clots, angiogenesis, & re-epithelialization ⁽⁹⁾.

Types of topical insulin application

Topical insulin application for wound healing dates back to 1960s & 1970s. Application of topical insulin to heal wounds declined next that time, however few researches were conducted till late 1990s ⁽⁶⁾. Local injection, sprays, cream, & dressings have lately been used successfully to treat diabetic & non-diabetic wounds. Moreover, with advancement of more advanced technologies for long-term release of bioactive insulin, topical insulin has maintained its popularity ⁽¹⁰⁾.

Intralesional insulin solution

Normal saline & betadine were used to clean ulcers & erosions. With insulin syringe and spray 0.5-1ml insulin over each ulcer ⁽¹¹⁾. Ulcers are then wrapped in sterile gauze. Blood sugar levels before & after treatment were tested. Everyday twelve hourly such two sittings were performed, whereas disease-specific treatment remained unchanged ⁽¹²⁾.

Advantages of intralesional insulin

Across changing inflammation, accelerating epithelialization, & neovascularization, intralesional insulin usage can enhance wound closure, decrease wound healing time, & enhance wound remodeling ⁽¹⁰⁾. There were no adverse systemic & local impacts reported ⁽⁶⁾.

Intralesional insulin in oral lichen planus (OLP)

Although OLP is not hereditary disease, it is believed to be linked to cell-mediated immunity. Because OLP is thought to be T cell-mediated disease with Th1 cytokine imbalance, most therapeutic

interventions have aimed to target inflammatory route underlying OLP. Local suppression of T cells & decrease in release of cytokines like TNF & IFN are particularly important in OLP management⁽¹³⁾. Earlier research showed that insulin could decrease inflammation & rise collagen deposition, resulting in faster burn wound healing. As a result, insulin could play role in healing of wounds & ulcers in erosive type OLP⁽¹⁴⁾. Intralesional insulin injection's biological impacts have been linked to number of molecular mechanisms. a) Insulin deactivates NFκBp50/p65 to reduce inflammation through increasing glucose uptake, b) Insulin induces fatty acid biosynthesis & thus inactivates TNFα mediated inflammatory paths, c) Insulin promotes cell survival by containing protein synthesis & inhibiting proteolysis via FOXO inactivation, d) Insulin acts as growth factor & can stimulate same signaling way to decrease inflammation, & e) Insulin modulates inflammation by decrease of proinflammatory cytokines & containing anti-inflammatory cytokines⁽¹⁵⁾.

The nature of the action of insulin in acne and other skin diseases, however, is obscure. Even through persistent clinical impression that high sugar intake is harmful to acne, belief that appears to be based on known aggravation of pyogenic infections by glucose, it appears unlikely that elevated blood glucose levels are of etiological significance. There is no clear evidence of consistent blood glucose abnormalities in acne, dietary carbohydrate differences do not appear to impact course of disease, & juvenile diabetics do not appear to have rising incidence of acne⁽¹⁶⁾. In study of **Soyuduru et al.**⁽¹⁷⁾ reported that impact of insulin was most likely independent of blood sugar levels. However, it appears plausible that insulin may enhance acne through its peripheral impact on cellular carbohydrate metabolism.

Advancement formed by insulin & reverse impact of glucagon, both of which have local influence, & substance to this viewpoint. It's worth noting that estrogens & thyroid extract, 2 clinically useful hormonal substances for acne management, are thought to impact carbohydrate intermediary metabolism. **Matschinsky and Wilson**⁽¹⁸⁾, working with mouse ear epidermis, discovered that estrogens stimulate glucokinase enzyme system, resulting in greater glucose absorption by cell. **Kreilmeier-Berger et al.**⁽¹⁹⁾ has demonstrated that 1-thyroxine enhances glucose as simulation & aerobic glycolysis in guinea-pig whole skin preparations. Failure of intralesional insulin to affect delayed responses indicates that local impact of insulin is to some extent specific for acne inflammation & does not support notion that delayed tuberculin allergy plays role in pathogenesis of acne. Improvement of acne & delayed allergic reactions by glucagon suggest that pancreatic alpha cell hormone may increase inflammation in non-specific manner. When injected intradermally, it is clear that glucagon is not primarily irritating to normal skin. Just like controls for injected glucagon, glucose & saline

solutions are likely of limited utility. Substantial body of evidence suggests that insulin is quickly repaired by tissues, & persistent impacts of glucagon on inflammatory responses of delayed allergic reactions imply that it is similarly taken up by tissues. Glucose & sodium chloride, on other hand, are freely diffusible substances that will most likely leave injection site rapidly⁽²⁰⁾.

Insulin changes inflammation by reducing pro-inflammatory cytokines & stimulating anti-inflammatory cytokines

Insulin stimulates STAT3 by PI3/Akt pathway that inhibits STAT1 synthesis & induces class shifting of M1 to M2 macrophages that heal macrophages that function in constructive processes such as tissue & wound healing. M2 macrophages as well generate polyamines & ornithine via arginase paths, as well as anti-inflammatory cytokines IL-4, IL-10, & IL-13⁽²¹⁾. Insulin, in conjunction with M2 macrophages, stimulates IP3K/Akt paths, which promotes wound healing by inducing protein & fatty acid biosynthesis, cell division, cell migration, & angiogenesis. Adipocytes generate cytokines such as IL-13, which stimulates activation of alternative & M2 macrophages. M2 & alternatively activated macrophages secrete anti-inflammatory cytokines as IL-10 & may secrete insulin-sensitizing features such as PPAR-γ, creating vicious circle for insulin activity. Anti-inflammatory cytokine IL-10 can be activated by PPAR-γ⁽²²⁾. MMPs were found in very large concentrations in non-healing human wounds. There is difference in expression of pro-inflammatory cytokines & their inhibitors, proteases & their anti-proteases in chronic & inflamed wounds⁽²³⁾.

Topical application of insulin for wound healing dates back to 1960s & 1970s. Topical insulin has lately been used successfully to heal diabetic & non-diabetic wounds. Moreover, with advancement of more progressive materials for long-term release of bioactive insulin, topical insulin has maintained its popularity⁽⁶⁾. Earlier pilot research was conducted to assess impact of topical insulin on decubitus ulcers. By fifteenth day, there was important variation in wound healing rate among cure & control groups, with no adverse events & hypoglycemia⁽²⁴⁾.

Intralesional application of insulin on skin wounds promotes keratinocyte migration, hastens re-epithelialization, & boosts fibroblastic response. Insulin-induced keratinocyte migration & distinctions are insulin receptor-dependent, but not EGFR-dependent. Additionally, this impact is mediated via PI3K-Akt-Rac1 paths⁽²⁵⁾. Randomized studied case-blind placebo-controlled interventional research concluded that topical insulin treatment was safe, efficacious, inexpensive, & easily accessible therapy option for chronic trophic ulcers in leprosy studied cases⁽²⁶⁾. **Gaspar et al.**⁽²⁷⁾ evaluated the potential of intralesional insulin as an inducing agent in

the regeneration of wounds that are difficult to heal like therapeutic option. Results of insulin therapy has been shown to be effective and without adverse effects. **Pawar**,⁽¹¹⁾ reported that topical intralesional insulin was used to cure non-healing pemphigus vulgaris erosions & ulcers. Ulcers had recovered significantly after two weeks. All of ulcers & erosions had recovered completely with dyspigmentation by end of fourth week. Research discovered that topical insulin application is simple & cost-effective cure for pemphigus ulcers & erosions. Another earlier research that looked at impact of intralesional insulin on acne vulgaris found that insulin enhances condition. Contrary to previous research, intralesional insulin appears to be more effective than parenterally injected insulin because systemic impacts of parenterally injected insulin, particularly stress of insulin shock, were prevented⁽²⁸⁾.

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