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Review

Receptor phenomena and signaling pathways in the use of low doses insulin as a bio-restructuring agent in Aesthetic Medicine: promotes biological aging. Meta-analysis and systematic review of the literature

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Abstract. The method of using low-dose insulin is indicated by some authors in aesthetic medicine as a technique for the bio-restructuring of tissues through the dermo-epidermal mesotherapy technique also in the areas of the face, neck and décolleté. The result of this off-label method will be that of an apparent aesthetic improvement, but with the formation of scar tissue and fibrosis in the injection tissue as well as in the surrounding tissues due to the inflammatory stimulus on the target cells and an excess production of Extracellular Matrix (ECM) deposited by fibroblasts with the formation of fibrotic tissue. In this meta-analysis and review of the literature, we delve into the mechanism it produces through which it triggers these effects and the aging process triggered through fibrosis in the tissues. Attention is also paid to any dosages and characteristics of the different types of insulins which can give different results up to the possible phenomena of pharmacological intolerance. This procedure will exclusively result in biological aging of the tissues.

Key words: insulin low dose, growth factors, neocollagenogenesis, fibrosis

Introduction

Continuous research in aesthetic medicine to improve interventions in the dermis in order to reduce the damage of chrono and photo-aging through physiological neocollagenogenesis by personalizing interventions on the patient, leads to the use, albeit off label, of some chemical elements (molecules or substances) aiming to improve the normal aging process[1]. One of the methods used to improve the signs of dermal-epidermal aging recommends the use of insulin in low doses. The aim of this review is to investigate which biological activity insulin carries out on cells, on fibroblasts and in the extracellular matrix, highlighting which type of neocollagenogenesis is activated through its use, albeit at low doses.

The scientific literature agrees in defining multiple properties and functions of type I and type III collagen in the dermis[2] (Figure 1). Young skin has a greater amount of type III than type I and with the passage of time the trend is bound to reverse[3]. The Extracellular Matrix (ECM) (Figure 2) facilitates signaling phenomena on the cells immersed in it and all the cells of the organism have the property of receiving and transferring signals through specific ligands. Hormones, cytokines and even electrolytes (Na, K, Ca, Mg) generate and allow the propagation of signals within cells through the expression (binding) on their external membrane receptors with nanomolar (high) affinity in specific tissue[4]; fibroblasts are also sensitive to these signals due to the expression of membrane glycoproteins on their surface[5].

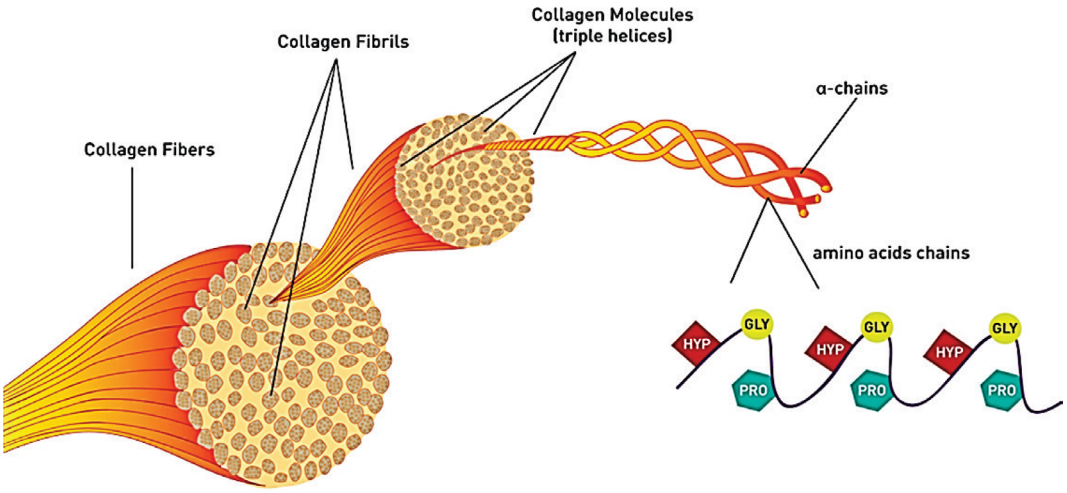

Figure 1. Collagen fibers.

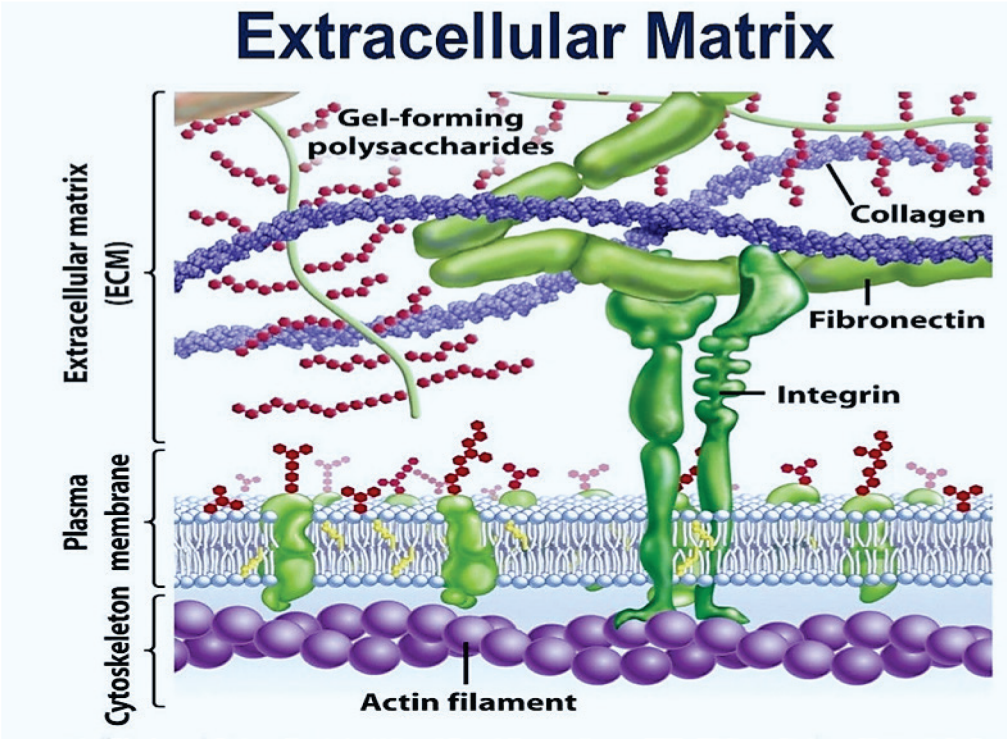

Figure 2. Extracellular Matrix.

Meta-analysis of the literature

We used the main search engines such as PubMed and Google Scholar to check whether there were publications and a protocol from the international scientific community regarding the off-label use of insulin in aesthetic medicine to improve the signs of epidermal skin aging, but we did not find any published articles. The primary hypothesis that low doses of insulin can have a positive effect in the dermis to justify its off-label use is based on the biological mechanism that this drug stimulates cells due to its hormonal

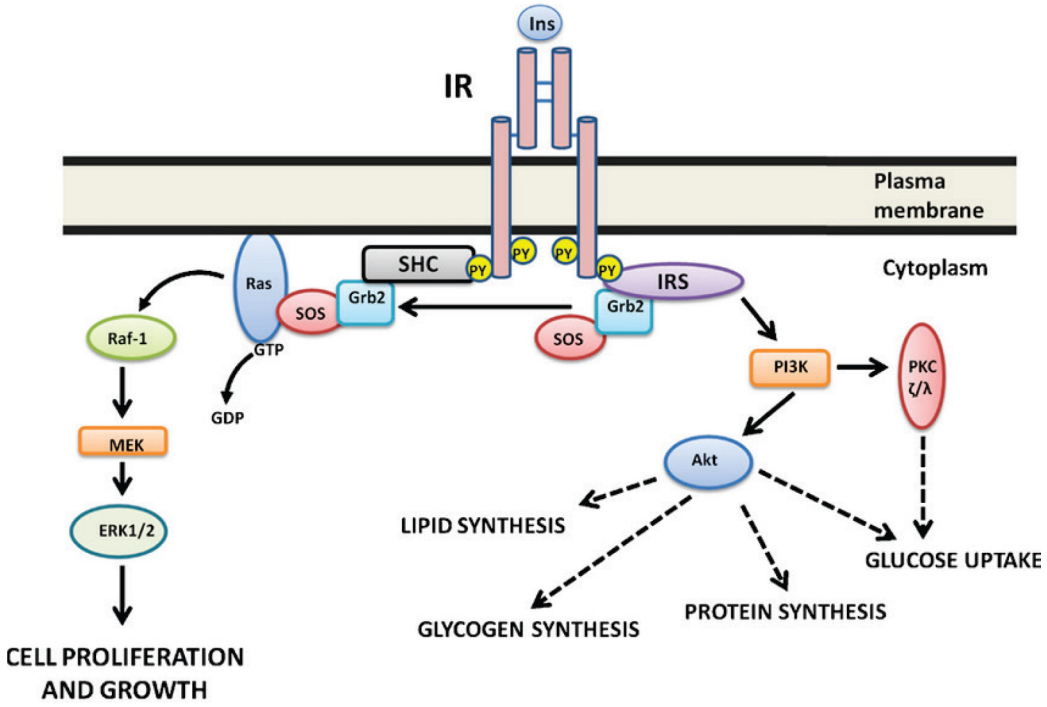

Figure 3. Nuclear Receptors of Insulin and pathway of signal cascade in mammalian cells.

activity. In fact, some articles state that insulin has an improving role on surgical scars[6]. Insulin is the hormone mainly responsible for the uptake, control of storage and use of glucose, amino acids and fatty acids and binds to specific receptors[7]. Insulin regulates the transcription of specific genes through those specific receptors[8] (Figure 3). Insulin belongs to a family of interrelated peptides called Insulin-Like Growth Factors (IGFs) (Figure 4), which have a stimulating capacity; IGFs are produced in many tissues. The insulin family consists of insulin, insulin-like growth factor 1 (IGF-1), insulin-like growth factor 2 (IGF-2), their receptors (IR, IGF-1R and IGF- 2R) and their binding proteins[9]. On cells, the receptors for insulin and for IGF-1 and IGF-2 are closely related and insulin is able to bind to the IGF-1 and IGF-2 receptor by affinity and in reverse direction[8]. After binding, anabolic actions are activated and include a stimulation of the use and intracellular storage of glucose, amino acids, and fatty acids, while catabolic processes are inhibited[8,10]. As a consequence, an excess of ECM deposition is produced[9]. It is known that the deregulation or dampening of IGF-1 activity has positive effects on cellular longevity[11], and how an increase in the stimulation of IGF-1R decreases the vital capacity of cells. This mechanism is well conserved from yeast to human cells[12]. The mitogenic activity of insulin occurs through an alteration in the velocity of expression of specific genes with consequent transductions of specific mRNAs[8,10] (Figures 3-4) which occur within seconds or at most minutes[8]. The target cell allows the initiation of actions triggered by insulin through a receptor located on its surface. Every mammalian cell has this receptor on its surface with a great variability in number: from 40 on erythrocytes to 300,000 on adipocytes[8] (Figure 5).

Through the insulin receptors present in fibroblasts and their expression, the production of inflammatory cytokines and their proliferation are activated by means of tyrosine protein kinases[13]. Through the activation of the insulin receptor expressed on the cell surface, some effects on gene transcription are triggered rapidly while others relating to protein synthesis, proliferation and cell differentiation may require a few days[8]. The biological mechanism has the same[14] characteristics that are observed through the stimulation of the Epidermal Growth Factor (EGF), Insulin Growth Factor (IGF-1) and Platelet Derived Growth Factor

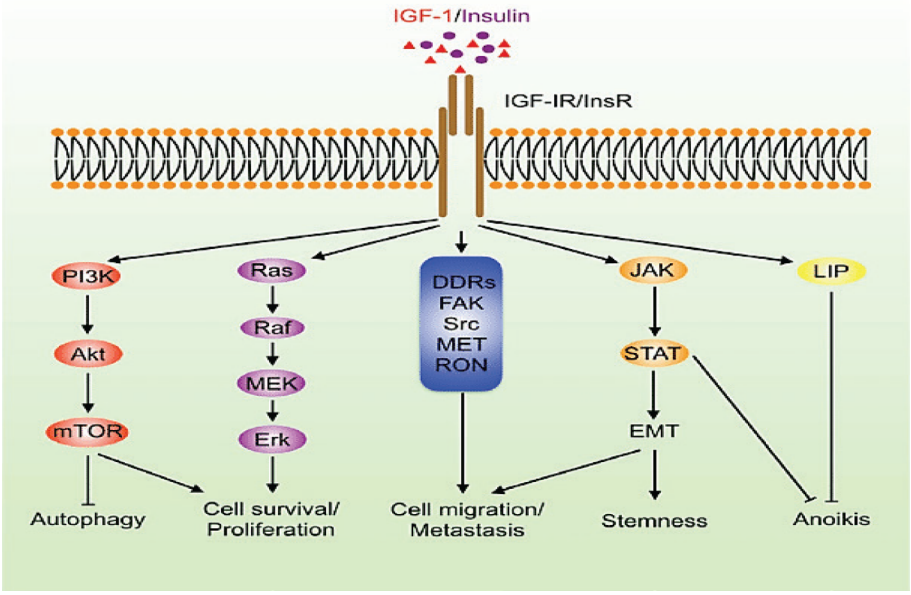

Figure 4. Insulin Growth Factor Receptor (IGF-R) on every mammalian cell.

Target cells for IGFs include:

(1) Fibroblasts
(2) Adipocytes
(3) Osteoblasts
(4) Chondrocytes
(5) Muscle cells

Figure 5. Target of IGFs.

(PDGF). A single molecule of insulin is sufficient and necessary to activate its action as a growth factor[12], as it is capable of independent existence and activity and is the smallest chemical unit that preserves the chemical characteristics of the substance itself. The binding of the hormone to the receptor induces rapid intramolecular autophosphorylation which is autocatalytic, resulting in an increase in tyrosine kinase activity, necessary for signal transduction (Figure 3). Following the stimulation of kinase activity, a series of events are triggered, involving the phosphorylation of Insulin Receptors 1, 2, 3, and 4 (IRS 1-4)[8]. Phosphorylated IRS-2 serves as an attachment for the so-called Src homology 2 domains. One of these proteins is a phosphoinositide-3-kinase. The latter is activated by numerous molecules that stimulate mitogenesis including PDGF, EGF and interleukin-4. Not only that, phosphatidylinositol 3-kinases (PI-3-kinase) functions as a second messenger by activating the Protein 70 (p70) and Protein Kinase B or PKB, which is a cytosolic protein that plays a key role in the PI3K\Akt pathway with gene transcription, enzymatic activity and protein translocation. Therefore, insulin activates Mitogen-Activated Proteins (MAP kinases), which are closely related to the switch oncoproteins called Ras. The activation of tyrosine kinase receptors activates the Grb2 protein, which in turn binds to Son of Sevenless (SOS), which is a guanine nucleotide exchange factor, which activates Ras, activating the serine-threonine kinase (Raf1) and therefore the MAP kinases. The activation cascade of these signals allows the activation of early response genes and cell growth through the synthesis of new DNA (Figures 3-4)[8].

The cells of the papillary dermis (Figure 6) of mammals produce IGFs, but during the aging process there is a progressive decrease and even inability to produce IGF by the cells of the papillary dermis[15]. Furthermore, the Reacting Oxygen Species (ROS) that

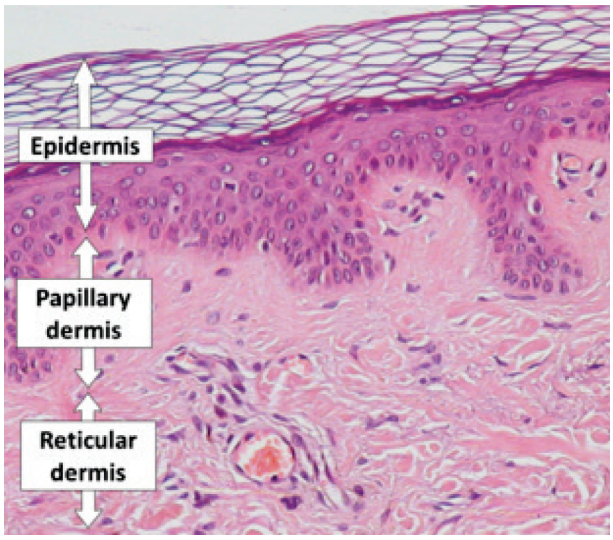

Figure 6. Papillary Dermis.

accumulate in the tissues during the aging process, in addition to being a source of damage to the cells of the papillary dermis, act as a brake on the sensitization of adjacent cells to IGF, with consequent alterations of the signaling processes[16]. These pathophysiological considerations alone do not allow us to validate low-dose mesotherapy insulin supplementation even with an off-label indication, even if exclusively on patients in whom it is intended to induce tissue fibrosis, given the activation of insulin's inflammatory cytokines[13] and considered fibrotic neocollagenogenesis[17]. In fact, given the lack of a biochemical parameter to use on the patient, even in low-dose, using it is always necessary to keep in mind the spill-over phenomenon with possible manifestations in the tissues that do not constitute the target of the treatment[18] and the possible prediction of drug toxicity in the tissue[19]. In fact, in the tissues subject to low-dose mesotherapy supplementation, an increase in insulin concentration can lead to an increased risk of the formation of atherosclerotic plaques at the level of the arterioles of the areas of the dermis subjected to the treatment, due to its mitogenic activity[8,20], even after predictable effects of hypoxia on the arterioles of the dermal papillae and a decrease in tissue capacity. It can trigger the production of anti-insulin IgG antibodies[8], with possible systemic implications. It can mediate allergic-type manifestations triggered locally by IgE, due to one of the components added in the formulations, such as protamine, Zn2+, phenol, etc.[8]. Furthermore, the possibility that part of the insulin may be absorbed by the systemic circulation raises the risk of the development of a metabolic syndrome in predisposed subjects[21], even taking into consideration the weight of the anatomical area to be treated alone, keeping in mind that the correct therapeutic use of insulin in a normal healthy and slim subject is equal to 0.2/0.5 U per kilogram of body weight[22]. Short-acting insulin analogs produce molecular and biological effects similar, but not identical, to those of slow-acting insulin. Compared to rapid insulin, long-acting analogues activate the Extracellular signal-Regulated Kinase (ERK) pathway more intensely via both Insulin Receptor-A (IR-A) and IGF1R and initiate greater cell proliferation. Thus long-acting analogues activate the mitogenic signaling pathway more effectively than rapid insulin and cause an increase in cell proliferation[23].

It is also necessary to consider that the local concentration of insulin is determined by the role of the absorption phenomenon, which can be modified simply by a change in ambient temperature or by differences in local blood flow[24].

Conclusion

According to this review, the off-label administration of low-dose insulin used in aesthetic medicine activates type I neocollagenogenesis with the formation of scar tissue[16] due to the inflammatory cascade it produces locally[13], and generates fibrosis and different effects cannot be ruled out upon prolonged use, even potentially more intense if slow-release insulins are used.

Further clinical studies are necessary, but also histological studies on the healthy tissue, in order to make the therapeutic indication safe.

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