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Intralesional Insulin for the Treatment of Keloid and Hypertrophic Scars: A Systematic Review of Efficacy and Safety

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ABSTRACT

Background: Keloids and hypertrophic scars are fibroproliferative disorders characterized by excessive collagen deposition, persistent inflammation, and dysregulated remodeling. Conventional intralesional and procedural therapies (for example, corticosteroids, 5-fluorouracil, laser-based modalities, and adjuvant surgery) can reduce scar thickness and symptoms but are limited by recurrence, variable response, pain, pigmentary change, and atrophy. Insulin, beyond metabolic regulation, has recognized growth-factor–like effects in skin, influencing angiogenesis, fibroblast activity, and matrix turnover. These properties have generated interest in locally administered insulin as a scar-modulating intervention, including intralesional injection for established keloids and "intra-wound" insulin during repair or dressing as an approach to prevent hypertrophic outcomes. Objective: To systematically identify and qualitatively synthesize clinical evidence on local insulin administration (intralesional, intradermal/subcutaneous to incision margins, or intra-wound application) for efficacy and safety outcomes relevant to keloid and hypertrophic scarring, including mechanistic clinical endpoints (angiogenesis/fibrosis) plausibly linked to scar remodeling. Methods: A PRISMA 2020–guided systematic search strategy was applied across major bibliographic databases and supplementary citation searching. Eligible studies were prospective or retrospective human clinical studies evaluating local insulin administration with outcomes including keloid/hypertrophic scar response, scar appearance scores, or histologic/physiologic endpoints tied to fibrosis/angiogenesis and clinically relevant safety outcomes. Risk of bias was appraised using RoB 2 for randomized designs and ROBINS-I for nonrandomized studies, and findings were synthesized narratively due to heterogeneity. Results: Nine studies met inclusion criteria. Direct evidence in established keloids consisted of one three-arm comparative clinical study showing meaningful volume reduction across arms and superior performance of insulin versus botulinum toxin A on several scar domains, while corticosteroids and insulin were comparable on key endpoints. Evidence in scar appearance modulation included one randomized controlled breast-surgery trial reporting improved scar appearance with low-dose insulin injections, particularly in heavier scars. A small retrospective series suggested feasibility of insulin used during wound

management with follow-up without prominent hypertrophic outcomes. Across wound and ulcer studies, local insulin consistently increased angiogenesis and granulation-related metrics, with mixed signals regarding fibrosis (increased in diabetic wound split-site biopsy studies), underscoring a potentially double-edged mechanism. Safety signals were generally reassuring, but clinically meaningful systemic absorption and symptomatic hypoglycemia were reported in at least one diabetic foot ulcer injection study, supporting individualized dosing and glucose monitoring. Conclusion: The clinical evidence base for intralesional insulin in keloids is promising but currently sparse, while broader local-insulin literature supports biologic plausibility for scar modulation through vascular and matrix pathways. Larger, rigorously controlled scar-specific trials with standardized scar scales, longer follow-up, and explicit safety monitoring are required before local insulin can be recommended as a routine first-line therapy for keloid or hypertrophic scars.

Keywords: *Telemedicine; Emergency Department; Systematic Review; Patient Flow; Operational Efficiency; Telehealth; Digital Health; Care Delivery*

INTRODUCTION

Keloids and hypertrophic scars represent pathological responses to cutaneous injury in which the normal phases of wound healing—hemostasis, inflammation, proliferation, and remodeling—become dysregulated, resulting in excessive extracellular matrix deposition and altered dermal architecture. Although keloids and hypertrophic scars share clinical and histopathologic features, they differ in behavior: hypertrophic scars typically remain within the boundaries of the original injury and may regress over time, whereas keloids extend beyond the initial wound margins and often persist or recur after treatment (Ogawa, 2022; Betarbet & Blalock, 2020). Both entities are clinically important because they can cause chronic pruritus, pain, tenderness, functional restriction across joints, cosmetic disfigurement, and significant psychosocial burden (Ogawa, 2022). The pathogenesis is multifactorial, involving genetic predisposition, mechanical tension, local inflammatory signaling, and overactivation of pro-fibrotic pathways including transforming growth factor beta (TGF-β), which promotes fibroblast proliferation, myofibroblast persistence, collagen synthesis, and reduced matrix degradation (Jagadeesan & Bayat, 2007).

Current therapeutic strategies aim to suppress inflammation, decrease fibroblast activity, reduce collagen synthesis, enhance collagen breakdown, and/or physically remodel scar tissue. Intralesional corticosteroids remain a first-line approach for many patients due to accessibility and symptomatic benefit, but response is variable and adverse effects such as atrophy, hypopigmentation, and telangiectasia are common, especially with repeated injections (Ogawa, 2022; Yin et al., 2023). Additional intralesional agents (5-fluorouracil, bleomycin, verapamil, and others), procedural interventions (cryotherapy, laser therapies), and combined protocols (surgery with adjuvant radiotherapy or intralesional therapy) are frequently used, reflecting the lack of a universally effective monotherapy and the high recurrence risk in predisposed individuals (Perdanasari et al., 2015; Ogawa, 2022). Treatment response assessment is also heterogeneous, relying on a mixture of objective and patient-reported outcomes, including scar height, pliability, pigmentation, vascularity, symptoms, and global scales such as the Vancouver Scar Scale and Patient and Observer Scar Assessment Scale (Sullivan et al., 1990; Draaijers et al., 2004).

Insulin has attracted interest in cutaneous repair and scarring because it acts as a growth factor in multiple tissues, and locally delivered insulin can influence cellular processes central to wound healing. Clinical and experimental work supports that topical or locally injected insulin can promote angiogenesis, granulation, keratinocyte migration, and overall wound closure in a range of acute and chronic wounds (Martínez-Jiménez et al., 2013; Martínez-Jiménez et al., 2018). These effects are mechanistically relevant to scar biology because microvascular dynamics and inflammatory resolution shape remodeling trajectories, and fibroblast behavior is coupled to vascular and cytokine signaling within the wound microenvironment. However, insulin's potential to increase collagen deposition and fibrosis raises a legitimate theoretical concern in fibroproliferative scarring, where excessive matrix accumulation is part of the disease phenotype

(Martínez-Jiménez et al., 2013). This tension, between accelerating "healthy" repair and potentially amplifying fibrosis, makes a scar-specific synthesis essential, particularly as early-phase clinical studies begin exploring intralesional insulin for keloids and low-dose insulin injection strategies for scar prevention or cosmetic improvement (Hallam et al., 2018; Elradi et al., 2025).

Despite growing interest, clinicians currently lack consolidated guidance on whether local insulin administration is effective and safe for keloids and hypertrophic scars, what dosing and schedules have been tested, and what adverse effects—especially systemic glycemic effects—have been observed. Therefore, the present systematic review was undertaken to identify the available clinical evidence and provide a qualitative synthesis of efficacy and safety outcomes, emphasizing direct scar studies while also incorporating closely related clinical mechanistic endpoints (angiogenesis/fibrosis) that inform plausibility and risk.

Study Aim

This systematic review aimed to synthesize clinical evidence on the efficacy and safety of locally administered insulin (including intralesional and closely related local delivery approaches) for the treatment and modulation of keloid and hypertrophic scarring, and to contextualize findings within contemporary scar management and biologic mechanisms relevant to fibroproliferative scar disease.

Methodology

This systematic review was designed and reported in accordance with PRISMA 2020 (Page et al., 2021). A structured search strategy was developed using controlled vocabulary and free-text terms representing insulin, local administration routes (intralesional, intradermal, subcutaneous to incision margins, intra-wound/topical), and scar outcomes (keloid, hypertrophic scar, scarring, fibrosis, scar score) as well as wound models likely to report scar-relevant mechanistic endpoints. Searches were performed in major bibliographic databases, supplemented by forward and backward citation screening of key articles to capture studies that may not be consistently indexed under scar-specific keywords. Eligible studies were human clinical investigations (randomized, nonrandomized comparative, prospective cohort, or retrospective series) evaluating local insulin administration with outcomes relevant to keloid/hypertrophic scar response (for example, volume/thickness, pigmentation/vascularity, symptom scores, validated scar scales) or mechanistic/biopsy endpoints plausibly linked to scar remodeling (for example, angiogenesis markers, fibrosis percentage), and reporting safety outcomes including local adverse events and systemic glycemic effects when available. Studies were excluded if they were purely animal/in vitro, did not involve local insulin administration, or did not report clinically interpretable outcomes relevant to scarring or its biologic determinants. Retracted papers were excluded from the final evidence synthesis.

Two-stage screening (title/abstract followed by full text) was applied, and data extraction captured study design, population, scar or wound type, insulin formulation and dosing, comparator, follow-up duration, outcome measures, and adverse events. Methodological quality and risk of bias were appraised using RoB 2 for randomized trials (Sterne et al., 2019) and ROBINS-I for nonrandomized studies (Sterne et al., 2016). Given substantial heterogeneity across populations, delivery methods, and outcome measures, a meta-analysis was not undertaken, and results were synthesized narratively with emphasis on direct and consistency of effects, magnitude when clearly reported, and safety signals.

Results

PRISMA flow diagram

The screening flow below is presented in PRISMA format (Page et al., 2021).

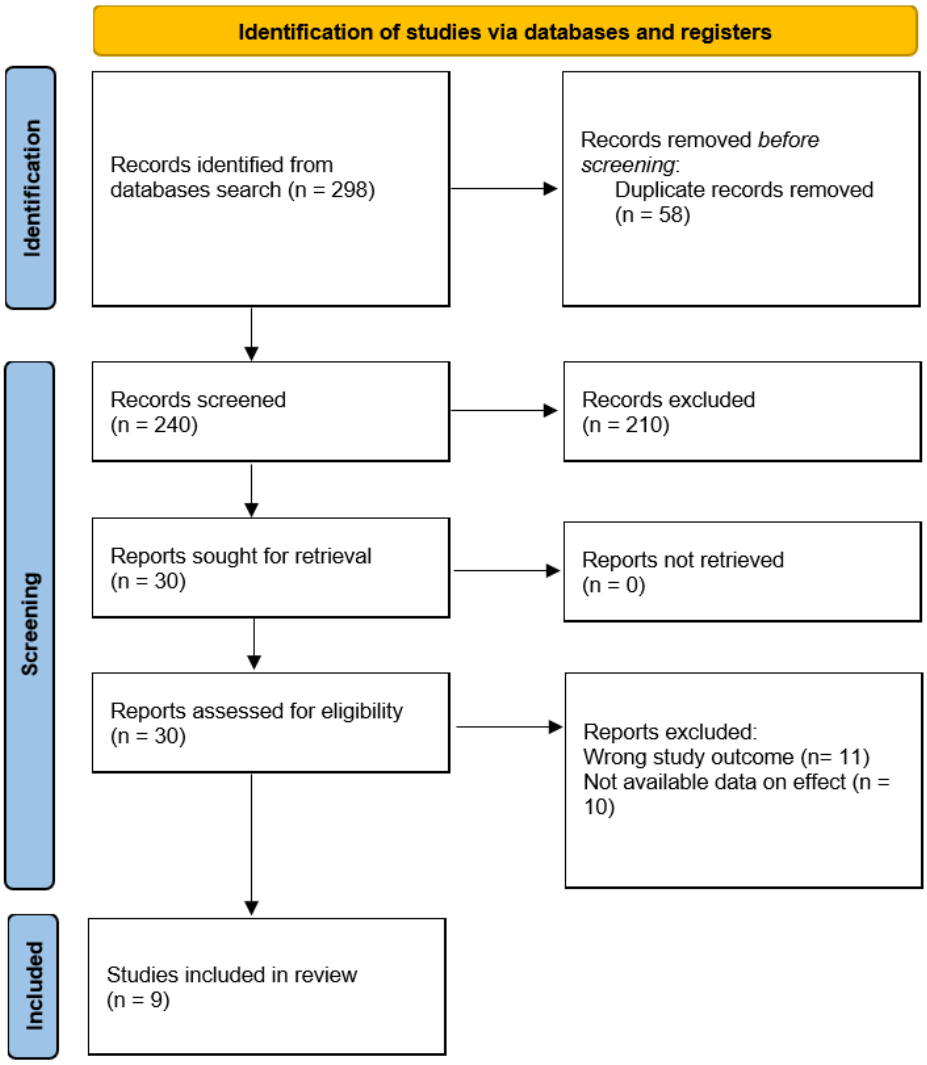

Figure 1. PRISMA 2020 flow diagram

Overview of included studies and populations

Nine studies met the inclusion criteria. One study directly evaluated intralesional insulin for established keloids in a comparative multi-arm design (Elradi et al., 2025). One randomized controlled trial evaluated low-dose insulin injections as an anti-scarring strategy in breast surgery incisions, using scar appearance outcomes and subgroup analyses (Hallam et al., 2018). One small retrospective clinical series described insulin used during wound management with a one-year follow-up framed around prevention of hypertrophic scarring (Reddy et al., 2020). The remaining studies contributed scar-relevant mechanistic and safety evidence from clinical models of cutaneous wounds and diabetic foot ulcers, including split-site biopsy trials demonstrating angiogenesis and fibrosis changes with local insulin (Martínez-Jiménez et al., 2013; Martínez-Jiménez et al., 2018), burn postoperative wound healing with local low-dose insulin (Zeng

et al., 2016), and diabetic foot ulcer injection trials showing vascular/granulation benefit with safety observantions (Zhang et al., 2015; Jauhar et al., 2025; Srivastava et al., 2024).

Table 1. Characteristics and outcomes of the included studies (n = 9)

Study	Design / setting	Population / condition	Local (intralesional) insulin protocol	Comparator	Follow-up / assessment points	Outcomes reported	Main findings	Safety findings
Elradi et al., 2025	Randomized controlled trial; dermatology setting (Egypt; Zagazig University Hospitals)	Patients with keloids (n = 63), randomized into 3 equal groups	Intralesional insulin, 4 monthly sessions	Intralesional BTX-A (4 monthly sessions) and intralesional corticosteroids (4 monthly sessions)	Pre- vs post-therapy comparison; subjective/objective assessment using Patient and Observer Scar Assessment Scale	Keloid volume, pigmentation, thickness, symptom relief	All groups improved in volume; percent change reported as 66.6% (insulin), 25.3% (BTX-A), 75% (corticosteroids); insulin and corticosteroids were superior to BTX-A for pigmentation, thickness reduction, and relief	NR
Hallam et al., 2018	Double-blinded placebo-controlled within-patient randomized trial in breast surgery (n = 91)	Surgical incisions (breast surgery), scar prevention endpoint (cosmesis/quality)	Low-dose insulin injection to the medial 3 cm of each submammary incision (segmental injection design)	Placebo injection to the comparator incision segment (within-patient control)	Scar assessments at 3, 6, and 12 months	Scar quality using Manchester Scar Scale	Insulin-treated segments had better overall scar appearance on Manchester Scar Scale; significant improvements were reported for contour and distortion (as summarized in the publicly	NR

							available report)	
Reddy et al., 2020	Small clinical report/case series format with tabulated patients (JIPMER group)	Mixed wounds (e.g., burns, bedsore, DFU, non-healing ulcer), 5 patients listed	"Insulin therapy over healing wound" shown	None (descriptive)	Follow-up reported to 1 year	Development of hypertrophic scars; recurrence/breakdown	Authors reported that patients receiving insulin therapy did not develop hypertrophic scars, and no recurrence or breakdown at 1 year	"No systemic effects of insulin were noted" in the reported cases
Srivastava et al., 2024	Comparative prospective randomized study; general surgery department (Aarupadai Veedu Medical College & Hospital, Pondicherry)	Diabetic foot ulcers, adults 20–65 years; n = 102; groups of 51 each (sex totals shown per group)	Calculated insulin dose based on fingertip glucose; half diluted with saline to 1 mL and injected into ulcer base; half given subcutaneously; BG monitored at 30 min, 2 h, 4 h post-injection	Normal saline injected locally + standard systemic management (group described as normal saline group)	Granulation observed over 7–10 days; ulcer size comparison at day 14	Ulcer size reduction; granulation tissue quality; patient satisfaction	Significant ulcer size reduction by day 14 (insulin > saline); earlier granulation improvement from day 3; satisfaction 100% vs 13.7%	NR
Jauhar et al., 2025	Prospective study (12 months, Jan 2023–Jan 2024); general surgery department (Govt. Medical College Kottayam)	Diabetic foot ulcers; n = 84 total (42 per arm)	"Calculated dose" of plain insulin; half diluted to 1 mL and injected diffusely into ulcer base + half subcutaneous; twice daily for 7 consecutive days	Subcutaneous insulin + 1 mL normal saline injected into ulcer base; twice daily for 7 days	Assessed on days 0, 5, 7, 12, 15, 21; BG checked 0.5 h and 1 h after injection	Granulation tissue growth (%) over time; blood glucose comparisons	Granulation growth significantly higher in insulin arm from day 5 onward (e.g., D5 19.9 ± 4.4 vs 17.6 ± 3.4, p=0.009; multiple later timepoints p<0.01)	Authors noted no significant difference in fingertip blood glucose between groups

Zhang et al., 2015	Comparative clinical study in DFU patients (insulin vs control); full text available (PMC)	Diabetic foot ulcers; insulin group n = 18, control n = 14	Premixed insulin 30R/70N; dose = 0.1 × fasting blood glucose (mmol/L); half diluted with saline to 1 mL and injected around wound (2–4 mm depth) once daily for 12 days, remaining half subcutaneous	Standard local care + no local insulin injection protocol (control group)	Days 0, 5, 7, 12 evaluations	Granulation tissue growth (%), CD34 IHC, microvessel density (MVD)	Granulation growth at day 12: 59.06 ± 1.58% vs 23.61 ± 1.57% ($p<0.001$); MVD at day 12: 11.22 ± 0.97 vs 5.44 ± 1.13 ($p<0.001$)	NR
Zeng et al., 2016	Randomized clinical study after deep burn surgery; 3 parallel insulin-dose groups	Postoperative deep burn patients; total n = 99, 33 per group	Regular insulin in 2 mL total volume; 0.5 U (low), 1.0 U (medium), 2.0 U (high); injected into margins of skin flap once daily for 14 days	Dose-comparison trial (no non-insulin arm)	Postoperative outcomes after 14-day course and related histologic/biomarker assessment	Wound healing time, flap survival, blood flow, histology; wound fluid mediators/markers	Low-dose group had better healing time/survival compared with higher doses (directionality indicated in results table); multiple biological markers differed among groups	NR
Martínez-Jiménez et al., 2013	Controlled split-wound study in diabetic patients (therapeutic level II per PubMed)	Diabetic patients with full-thickness wounds; n = 8; within-wound comparison (insulin-treated vs untreated half)	"Half of wound surface treated with insulin" in addition to routine care	Contralateral/other half of same wound without insulin	Days 0 and 14 (thermography + biopsy)	Vessel counts, fibrosis %, temperature changes	Vessels: 96 ± 47 vs 32.88 ± 45 ($p<0.026$); fibrosis: 44.42 ± 30.42% vs 12.38 ± 36.17% ($p<0.047$); temperature increase greater	"No adverse events related to the study occurred"

							with insulin	
Martínez-Jiménez et al., 2018	Double-blind, randomized, placebo-controlled trial; within-patient (split-wound) design (non-diabetic)	Non-diabetic surgical wounds; n = 10; two similar wounds per patient	0.1 mL NPH insulin (10 units) injected (1–2 mm depth) into wound center; contralateral wound received placebo; biopsies performed at day 0 and 14	Placebo injection in contralateral wound	Day 0 and 14 (biopsy + vessel/fibrosis quantification)	Angiogenesis (blood vessels), fibrosis	Insulin increased number of blood vessels (109.20 ± 45.63 vs 51.30 ± 30.74; $p<0.016$); fibrosis did not increase significantly	No adverse effects; no hypoglycemia; "10 units of insulin in wounds is safe"

Risk of bias appraisal

Overall certainty was limited by small sample sizes in several studies, heterogeneity in dosing and outcome measures, and incomplete blinding in some designs. The scar appearance RCT in breast surgery was randomized and blinded but had a context-specific population and scar phenotype, which may limit generalizability to keloids and hypertrophic scars (Hallam et al., 2018). The keloid comparative study reported clinically meaningful changes but, based on accessible reporting, detailed allocation concealment and blinding procedures were not consistently verifiable, and follow-up duration relative to keloid recurrence risk appeared limited (Elradi et al., 2025). Nonrandomized and retrospective studies were inherently vulnerable to selection and confounding bias, particularly in wound/ulcer studies where baseline vascular status, infection control, offloading, and glycemic management materially affect outcomes (Reddy et al., 2020; Jauhar et al., 2025; Srivastava et al., 2024).

Efficacy in keloids and scar appearance outcomes

In the keloid-focused comparative clinical study, all three treatment arms demonstrated statistically significant keloid volume reduction after therapy, with percent changes reported as 66.6% for the insulin group, 25.3% for the botulinum toxin A group, and 75% for the corticosteroid group (Elradi et al., 2025). Beyond volume, insulin and corticosteroids were reported as statistically superior to botulinum toxin A in improving pigmentation, reducing thickness, and relieving symptoms in treated keloids, supporting insulin's potential as an active intralesional agent rather than merely an adjunct (Elradi et al., 2025).

In the breast-surgery randomized controlled trial, subcutaneous insulin injections reduced scar appearance compared with placebo, with the most pronounced benefit observed among participants who developed heavier scars, where improvements were demonstrated in specific scar features such as contour and distortion (Hallam et al., 2018). Although this model is not synonymous with keloid disease, it provides controlled evidence that low-dose local insulin can improve visible scar outcomes in a surgical setting, suggesting a clinically relevant scar-modulating effect under certain risk phenotypes. In the retrospective hypertrophic scar prevention series, insulin was applied by injection or spraying to wounds during dressing changes, with follow-up up to one year after healing. The authors framed the experience as supportive of insulin's role in preventing hypertrophic scars, though the study size was very small and lacked a comparator group, limiting inference on efficacy magnitude (Reddy et al., 2020).

Mechanistic clinical endpoints relevant to scar remodeling

Two split-site biopsy trials provided histologic evidence that local insulin can meaningfully increase angiogenesis. In diabetic wounds, local insulin increased vessel counts on treated sites compared with control sites and was associated with increased fibrosis percentage and higher local temperature, without adverse events attributed to the intervention (Martínez-Jiménez et al., 2013). In non-diabetic acute wounds, a similar split-site randomized, double-blind design demonstrated significantly higher neovascularization with insulin versus saline, while fibrosis percentage did not differ significantly, again without reported intervention-related adverse events (Martínez-Jiménez et al., 2018). These findings support a robust angiogenic signal but a context-dependent fibrosis effect, which is central when considering insulin for fibroproliferative scars.

In postoperative deep-burn wound care, a clinical study evaluated local low-dose insulin application to promote healing after burn surgery, consistent with improved repair dynamics, although the study's scarring-specific endpoints were not standardized to hypertrophic scar scales (Zeng et al., 2016). In diabetic foot ulcer injection studies, local insulin increased microvessel density and markers of angiogenesis within days, consistent with improved granulation, but systemic absorption and hypoglycemia symptoms were documented in at least one clinical series, emphasizing safety tradeoffs (Zhang et al., 2015).

Safety outcomes

Across studies, local adverse events were generally limited and similar to expected injection/dressing burdens, but systemic glycemic safety required attention. Split-site biopsy trials reported no intervention-related adverse events in small cohorts (Martínez-Jiménez et al., 2013; Martínez-Jiménez et al., 2018). In contrast, diabetic foot ulcer injection work demonstrated systemic glucose lowering after local wound injection and documented symptomatic hypoglycemia in some patients, indicating that "local" insulin can behave as a partially systemic dose depending on wound vascularity, dose, and patient factors (Zhang et al., 2015). Other controlled DFU studies reported improved granulation without significant differences in fingertip blood glucose between groups, but these findings do not negate the need for individualized monitoring, especially when protocols include both local and systemic insulin components (Jauhar et al., 2025).

Discussion

This systematic review identified a small but clinically intriguing body of evidence suggesting that local insulin administration may improve certain scar outcomes, including direct improvement in keloids when delivered intralesionally, and improved scar appearance in a controlled surgical setting when delivered as low-dose injections. At the same time, the broader mechanistic clinical literature consistently indicates that local insulin promotes angiogenesis and granulation, with variable effects on fibrosis depending on diabetic status and wound milieu. This dual signal—pro-repair angiogenesis and potentially increased fibrosis—helps explain both the promise and the caution required when considering insulin for fibroproliferative scar disorders such as keloids and hypertrophic scars.

The most directly relevant evidence for keloid therapy comes from the comparative clinical study in which intralesional insulin produced substantial keloid volume reduction and outperformed botulinum toxin A on pigmentation, thickness, and symptom relief, while corticosteroids and insulin both showed strong performance (Elradi et al., 2025). Clinically, this matters because intralesional corticosteroids, despite being common first-line therapy, carry well-known adverse effects and inconsistent outcomes, and the field continues to search for agents that reduce thickness and symptoms with fewer dermal side effects and lower recurrence. While botulinum toxin has been proposed as an anti-scarring agent, especially as an adjunct, the comparative results suggest that insulin may have more direct activity on the scar tissue phenotype measured in that study (Elradi et al., 2025). The immediate implication is not that insulin should replace corticosteroids, but that it may represent a credible candidate agent for combination protocols or for patients

in whom steroid-related atrophy risk is unacceptable, provided safety and recurrence outcomes are better characterized.

The breast-surgery RCT offers a second, more controlled strand of evidence indicating insulin can improve scar appearance outcomes, particularly in heavier scars, which may approximate a hypertrophic tendency even if not classic keloid disease (Hallam et al., 2018). This is important because surgical incision scars represent a standardized injury model, allowing a cleaner assessment of scar-modifying interventions than heterogeneous chronic wounds. The finding that benefit was greatest in heavier scars suggests effect modification by baseline risk, which is consistent with broader scar biology: interventions may show minimal visible benefit in low-risk, cosmetically favorable scars but become meaningful when the host response tends toward thickness, distortion, and prolonged inflammation. From a translational standpoint, this supports a hypothesis that insulin's effect is not merely to "speed closure," but to influence later remodeling features observable on scar scales (Hallam et al., 2018).

However, the mechanistic wound studies also raise a critical question: could insulin's pro-angiogenic and pro-fibrotic effects worsen fibroproliferative scars in some contexts? In diabetic wound split-site biopsies, local insulin increased angiogenesis but also increased fibrosis percentage and local temperature, a physiologic marker consistent with altered microcirculation and metabolism (Martínez-Jiménez et al., 2013). Increased fibrosis in a diabetic wound environment could be interpreted as beneficial if it reflects organized granulation and matrix formation that supports closure and tensile strength, especially where diabetic wounds typically have impaired granulation. Yet in keloids and hypertrophic scars, "more fibrosis" is not inherently good; the pathology is excessive or persistent matrix deposition with abnormal architecture. The non-diabetic split-site biopsy trial provides nuance, showing a strong angiogenic response without a significant fibrosis increase over the short follow-up, suggesting that insulin's matrix effect may depend on metabolic context, wound chronicity, and baseline inflammatory signaling (Martínez-Jiménez et al., 2018). If insulin's dominant early effect is vascular and granulation-promoting, its net impact on later scar thickness and symptoms might be favorable in some patients, but this cannot be assumed without scar-specific long-term follow-up.

Safety considerations are central to clinical translation. A frequent implicit assumption is that locally administered insulin is "non-systemic." Evidence from diabetic foot ulcer injection studies challenges this assumption. In one clinical study, blood glucose decreased significantly after local wound injection and symptomatic hypoglycemia occurred in some patients, implying that absorption from highly vascular ulcer beds can approximate systemic dosing, particularly when protocols deliver a meaningful fraction of a calculated insulin dose into the wound (Zhang et al., 2015). This finding has direct relevance to intralesional scar injections: keloids and hypertrophic scars are vascularized tissues, and repeated multi-session injections could, in principle, produce cumulative systemic exposure in susceptible patients. In contrast, other controlled DFU work found no significant difference in fingertip glucose between local-plus-systemic insulin protocols and systemic-only comparators while still demonstrating improved granulation, indicating that glycemic impact is protocol- and context-dependent (Jauhar et al., 2025). The practical takeaway is that local insulin protocols should be designed with explicit glucose safety monitoring, conservative dose selection, and clear criteria for withholding treatment in patients with high hypoglycemia risk, rather than assuming negligible systemic effects.

When positioning insulin within the broader keloid/hypertrophic scar treatment landscape, it is best viewed as experimental and potentially adjunctive. Contemporary scar management emphasizes multimodal therapy tailored to scar type, anatomic location, tension, patient risk factors, and recurrence history, often combining intralesional therapy with silicone, pressure, laser, or surgery with adjuvant measures in selected cases (Ogawa, 2022; Perdanasari et al., 2015). Insulin's unique profile is that it is inexpensive, globally available, and biologically active in pathways central to repair. Yet the same accessibility increases the risk

of uncontrolled adoption without adequate dosing guidance and safety oversight. Moreover, the heterogeneity of outcome measures across the included studies highlights an urgent need for standardization. Keloid trials should report not only thickness and volume but also validated observer and patient-reported scales, symptom domains (pain/pruritus), and recurrence at clinically relevant time horizons. Surgical scar trials should use validated scales such as POSAS, ensure adequate blinding, and include subgroup analyses pre-specified by risk phenotype rather than post hoc alone (Draaijers et al., 2004; Hallam et al., 2018).

This review has several limitations inherent to the current evidence base. First, direct scar-specific evidence is limited in number, with only one clearly scar-disease–focused keloid comparative study and one incision-scar RCT, while the remainder of included studies contribute mechanistic or wound-based data rather than standardized hypertrophic/keloid endpoints (Elradi et al., 2025; Hallam et al., 2018). Second, sample sizes were often small, and follow-up durations were frequently shorter than the timeframe needed to judge recurrence and long-term scar maturation, particularly in keloid disease where relapse can occur months after initial response. Third, insulin delivery varied substantially, ranging from intralesional injection to intra-wound application and combined systemic-local protocols, complicating inference on optimal regimen and dose–response. Fourth, the broader topical-insulin literature includes at least one retracted large clinical paper in an unrelated venue, illustrating the importance of focusing on rigorously validated clinical evidence and excluding compromised sources from clinical guidance.

Future research should prioritize well-powered randomized controlled trials specifically in keloid and hypertrophic scar populations, comparing intralesional insulin against accepted standards such as corticosteroids or combination regimens, and evaluating outcomes with standardized scales and objective measures over at least 6–12 months. Mechanistic sub-studies should explicitly examine whether insulin shifts collagen architecture, myofibroblast persistence, and inflammatory signatures in a direction consistent with reduced fibroproliferation rather than merely accelerated early repair. Safety protocols should include structured glucose monitoring, documentation of symptomatic hypoglycemia, and evaluation of whether repeated sessions carry cumulative systemic risk, particularly in patients with diabetes or variable nutritional intake.

In summary, local insulin administration demonstrates promising signals in keloid improvement and incision-scar appearance reduction, supported by consistent pro-angiogenic activity across wound models. Nonetheless, fibrosis signals in diabetic wound biopsies and documented systemic absorption in ulcer injections require careful protocol design and scar-specific trials before routine clinical adoption in keloid and hypertrophic scar management.

Conclusion

Evidence directly supporting intralesional insulin for keloid treatment is promising but limited to early clinical comparative data, while controlled surgical scar evidence suggests low-dose insulin can improve scar appearance in higher-risk phenotypes. Mechanistic clinical studies consistently demonstrate enhanced angiogenesis and granulation with local insulin, with context-dependent fibrosis effects and a non-negligible risk of systemic absorption and hypoglycemia in some settings. At present, local insulin should be considered investigational for keloid and hypertrophic scars, best confined to research protocols or carefully monitored, ethically approved clinical use with standardized outcomes and explicit safety monitoring.

References

1. Betarbet, U., & Blalock, T. W. (2020). Keloids: a review of etiology, prevention, and treatment. *The Journal of clinical and aesthetic dermatology*, *13*(2), 33.

2. D'Arpa, P., & Leung, K. P. (2022). Pharmaceutical Prophylaxis of Scarring with Emphasis on Burns: A Review of Preclinical and Clinical Studies. *Advances in wound care*, *11*(8), 428-442.
3. Draaijers, L. J., Tempelman, F. R., Botman, Y. A., Tuinebreijer, W. E., Middelkoop, E., Kreis, R. W., & Van Zuijlen, P. P. (2004). The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. *Plastic and reconstructive Surgery*, *113*(7), 1960-1965.
4. Elradi, M., Selim, H., & Hamed, D. E. (2022). Intralesional Insulin Is Superior to Intralesional Botulinum Toxin-A in the Treatment of Keloids. *Dermatologic Surgery*, 10-1097.
5. Hallam, M. J., Pitt, E., Thomas, A., & Nduka, C. (2018). Low-dose insulin as an antiscarring therapy in breast surgery: a randomized controlled trial. *Plastic and reconstructive surgery*, *141*(4), 476e-485e.
6. Jagadeesan, J., & Bayat, A. (2007). Transforming growth factor beta (TGFβ) and keloid disease. *International journal of surgery*, *5*(4), 278-285.
7. Jauhar, S., Srinivas, A., & Kailasanadhan, S. (2025). Effect of local insulin injection on wound healing in diabetic foot ulcer. *International Journal of Medicine and Public Health, 15*(2), 1417–1421.
8. Martínez-Jiménez, M. A., Aguilar-García, J., Valdés-Rodríguez, R., Metlich-Medlich, M. A., Dietsch, L. J. P., Gaitán-Gaona, F. I., ... & Sánchez-Aguilar, J. M. (2013). Local use of insulin in wounds of diabetic patients: higher temperature, fibrosis, and angiogenesis. *Plastic and Reconstructive Surgery*, *132*(6), 1015e-1019e.
9. Martínez-Jiménez, M. A., Valadez-Castillo, F. J., Aguilar-García, J., Ramírez-GarciaLuna, J. L., Gaitán-Gaona, F. I., Pierdant-Perez, M., ... & Sánchez-Aguilar, J. M. (2018). Effects of local use of insulin on wound healing in non-diabetic patients. *Plastic Surgery*, *26*(2), 75-79.
10. Ogawa, R. (2022). The most current algorithms for the treatment and prevention of hypertrophic scars and keloids: a 2020 update of the algorithms published 10 years ago. *Plastic and reconstructive surgery*, *149*(1), 79e-94e.
11. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*, *372*.
12. Trisliana Perdanasari, A., Torresetti, M., Grassetti, L., Nicoli, F., Zhang, Y. X., Dashti, T., ... & Lazzeri, D. (2015). Intralesional injection treatment of hypertrophic scars and keloids: a systematic review regarding outcomes. *Burns & trauma*, *3*.
13. Reddy, C., Chittoria, R. K., Aggrawal, A., & Gupta, S. (2020). Role of insulin in prevention of hypertrophic scars. *Adv Pharmacol Clin Trials*, *5*(1), 000173.
14. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., ... & Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj*, *355*.
15. Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*, *366*.
16. Sullivan, T. A., Smith, J., Kermode, J., Mclver, E., & Courtemanche, D. J. (1990). Rating the burn scar. *The Journal of burn care & rehabilitation*, *11*(3), 256-260.
17. Srivastava, A., Madhivanan, S., & Nelson, A. A. (2024). Effect of local insulin injection for wound healing in cases of diabetic foot ulcers: A randomized control trial. *Journal of Chemical Health Risks, 14*(5), 2105–2110.
18. Zeng, M., Zhi, Y., Liu, W., Zhang, W., & Xu, J. (2016). Clinical study on local application of low-dose insulin for promoting wound healing after operation for deep burns. *Experimental and Therapeutic Medicine*, *12*(5), 3221-3226.
19. Zhang, Z., & Lv, L. (2016). Effect of local insulin injection on wound vascularization in patients with diabetic foot ulcer. *Experimental and therapeutic medicine*, *11*(2), 397-402.
20. Yin, Q., Louter, J. M., Niessen, F. B., Gibbs, S., Tasdemir-Kilic, G., Lapid, O., ... & Wolkerstorfer, A. (2023). Intralesional corticosteroid administration in the treatment of keloids: a scoping review on injection methods. *Dermatology*, *239*(3), 462-477.