

Systematic Review

Topical Insulin in Atrophic Acne Scarring: A Systematic Review of Efficacy, Safety, and Patient Satisfaction

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Abstract

Background: Atrophic acne scars are challenging to treat and have a negative psychological impact. Insulin has been tried as a topical adjuvant and stimulates fibroblast activity, collagen deposition, and keratinocyte migration. **Objectives:** To evaluate topical insulin for atrophic acne scars in terms of its effectiveness, safety, and patient-rated results. **Methods:** Five databases were searched for research on topical insulin, either alone or in conjunction with a procedure, without regard to the date. Records were screened, extracted, and evaluated in duplicate (RoB 2 or ROBINS-I) each by two independent researchers, using Covidence. **Results:** Fourteen studies with 619 patients, seven randomized and seven non-randomized, were qualified. All insulin arms improved from baseline (35.8% to 55.4%), but comparator arms mostly improved similarly; five studies, none at low risk of bias, favored insulin. Adverse effects were mostly local, minor, and transient, although one study reported systemic hypoglycemia-related symptoms; glucose monitoring was inconsistent, and satisfaction was high. **Limitations:** Meta-analysis was not possible due to heterogeneity in design, dosage, and outcome scales, and the small number of patients precludes certain conclusions. **Conclusions:** Although its superiority over current adjuncts has not been demonstrated, topical insulin appears to be an affordable, well-tolerated adjunct that may have a function where traditional therapies are unavailable; larger studies are needed.

Keywords: topical insulin; atrophic acne scars; acne scarring; microneedling; platelet-rich plasma; scar treatment; systematic review



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1. Introduction

Acne vulgaris is among the most prevalent dermatologic conditions worldwide, affecting about 8% of the population and 85% of adolescents [1]. Acne can persist or lead to scarring, resulting in significant psychological burden, including anxiety, depression, and reduced quality of life [2]. Post-acne atrophic scars arise from an imbalance of collagen degradation and synthesis during healing [3] and are classified into three types: ice pick, rolling, and boxcar, with ice pick being the most common [4]. These atrophic subtypes, together with raised hypertrophic and keloid scars, are illustrated in Figure 1 [5].

There is no single definitive treatment for atrophic scars. Current options include microneedling, laser therapy, platelet-rich plasma, dermabrasion, subcision, punch excision, chemical peels, and tissue augmentation. These have been associated with improvements

in scar appearance, but outcomes vary by scar subtype [6–8], and many require multiple sessions, carry significant side effects, and impose considerable cost [9].

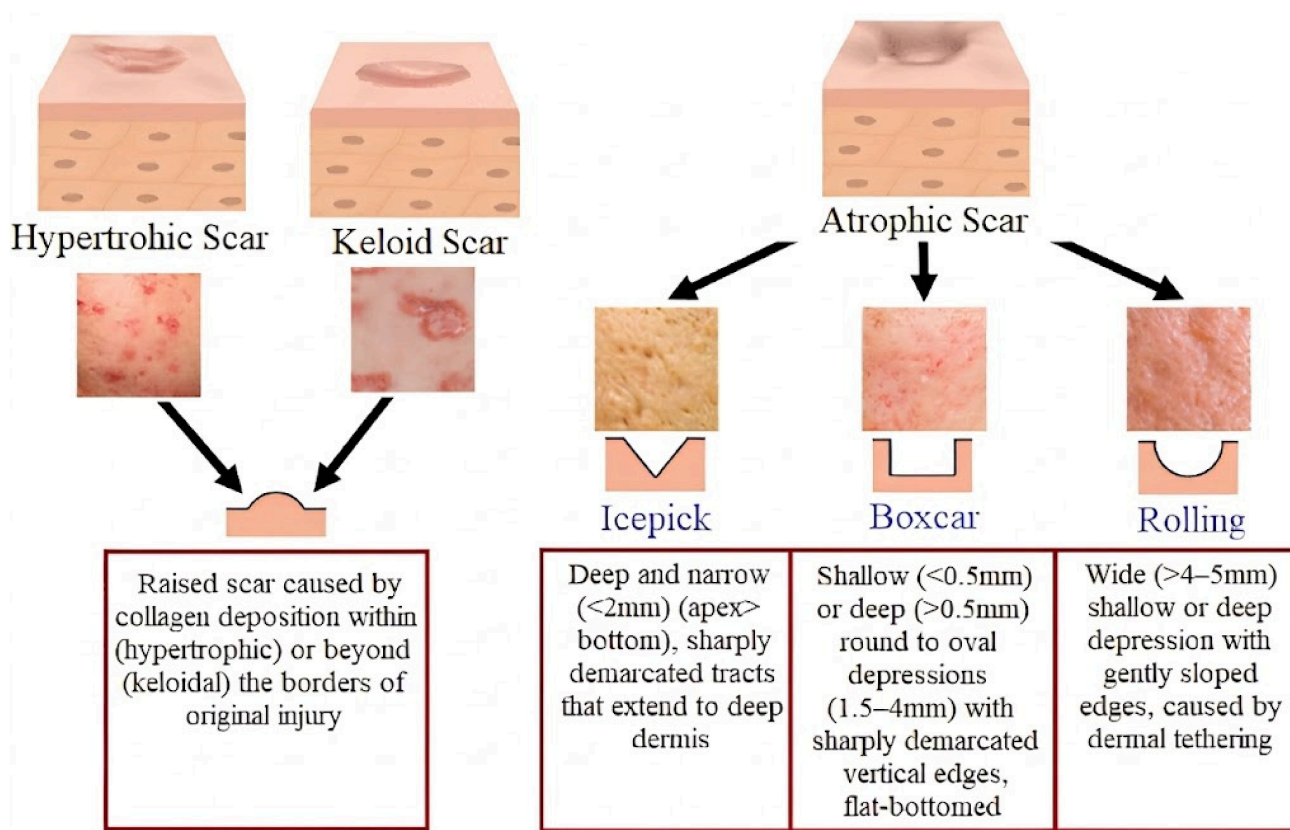


Figure 1. Classification of acne scars into raised (hypertrophic and keloid) and atrophic (ice pick, boxcar, and rolling) scars, with representative clinical images, schematic cross-sections, and defining features. Reproduced from Junayed et al. [5], published under a Creative Commons Attribution (CC BY 4.0) license.

Insulin has been linked to scar treatment through its regenerative effects, including improved keratinocyte proliferation, fibroblast activity, and collagen deposition [10]. It also enhances vascular endothelial growth factor (VEGF) expression, promoting angiogenesis [11]. Topical insulin enhances wound healing through multiple intracellular signaling cascades: binding to the insulin receptor (IR) activates the PI3K-Akt pathway. In keratinocytes, this drives re-epithelialization by inhibiting GSK-3 β , stabilizing β -catenin, and synthesizing laminin 332 and integrin α 3 β 1 [12–14]. In endothelial cells, Akt phosphorylates eNOS, stimulating NO production, vasodilation, and upregulation of VEGF and FGF-R [13]. In fibroblasts, TGF- β 1 upregulation promotes non-fibrotic repair through deposition of type 1 and 3 collagen with elastin [13,15] (Figure 2).

Previous systematic reviews have examined topical insulin as an adjunct to microneedling. This systematic review aimed to synthesize the current literature and assess the effectiveness of topical insulin as a treatment for post-acne atrophic scars, extending earlier syntheses by including randomized trials published in 2025 and 2026, by covering fractional CO₂ laser and micro-fractional radiofrequency delivery in addition to microneedling, and by stratifying outcomes according to scar morphology, Fitzpatrick phototype, and patient-reported satisfaction [16,17].

Molecular Mechanisms of Topical Insulin in Scar Treatment

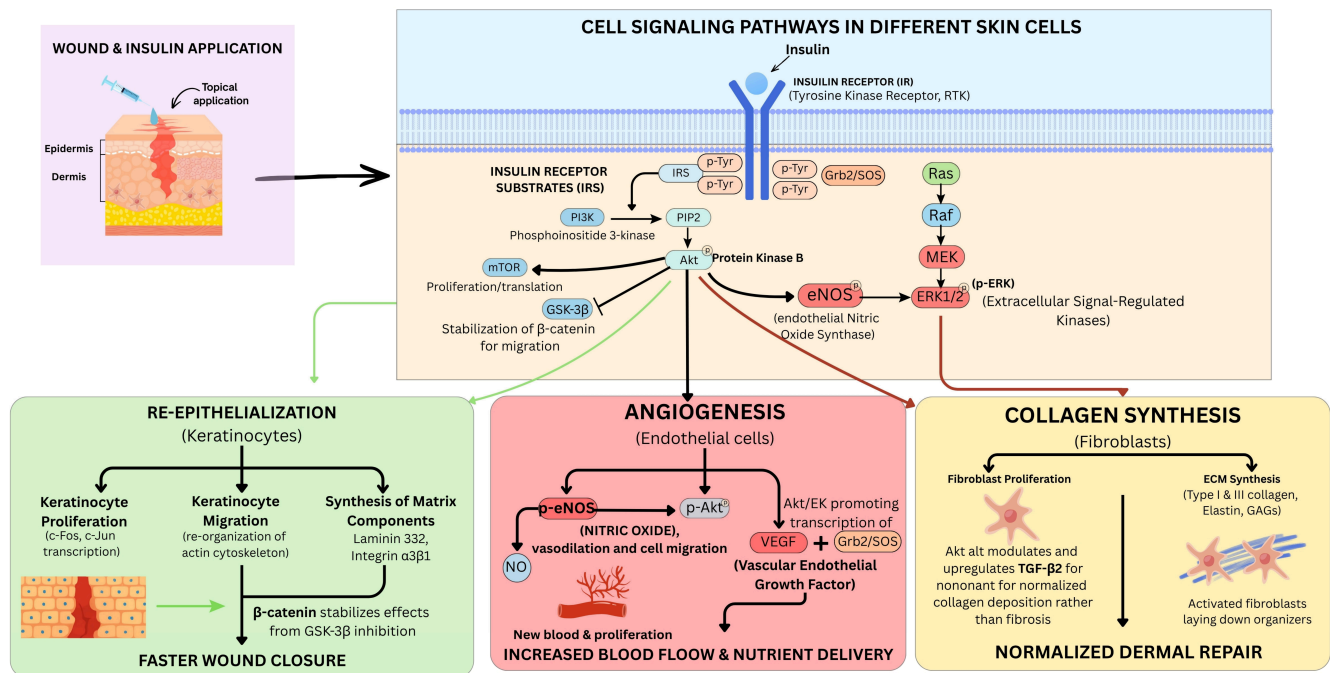


Figure 2. Molecular mechanisms of topical insulin in cutaneous wound healing. Footnote: IR: Insulin receptor; RTK: receptor tyrosine kinase; IRS: insulin receptor substrates; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; GSK3β: glycogen synthase kinase 3 beta; mTOR: mammalian target of rapamycin; Ras: rat sarcoma; Raf: rapidly accelerated fibrosarcoma; MEK: mitogen-activated protein kinase kinase; ERK1/2: extracellular signal-regulated kinases 1/2; Grb2/SOS: growth factor receptor-bound protein 2/Son of sevenless; VEGF: vascular endothelial growth factor; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; TGF-β: transforming growth factor beta; ECM: extracellular matrix; GAGs: glycosaminoglycans.

2. Materials and Methods

The systematic review protocol was registered in PROSPERO under registration number CRD420251061005. It followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline [18] (Supplementary Material S1).

2.1. Search Strategies

A comprehensive search was conducted across PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Google Scholar, without year restrictions. The initial search was run 13–27 May 2025 and updated on 7 September 2026, with the updated search date used for the final eligibility set. The updated search re-ran each strategy in full from database inception; its yield of 572 records therefore supersedes, rather than adds to, the 373 records of the initial search, and all 572 records, including the 148 retrieved from Google Scholar, were exported to Covidence (Veritas Health Innovation, Melbourne, Australia) and screened (Supplementary Material S2). Controlled vocabulary (MeSH in PubMed, Emtree in Embase) and free-text keywords were combined using Boolean operators to maximize sensitivity. All records were entered into Covidence [19], and duplicates were removed prior to screening (for the searching algorithm, refer to Supplementary Material S2).

2.2. Eligibility Criteria

PICO criteria were used to establish inclusion criteria (Supplementary Material S3). The studies had to be on the use of topical insulin as monotherapy or in combination, in

patients with clinically diagnosed post-acne atrophic scars regardless of gender, age, race, severity, and duration of scars. The studies had to have a control or comparator group and report at least one of the outcomes defined in Section 2.3. Eligibility did not depend on the direction, magnitude, or statistical significance of study results. Only English-language papers were included.

2.3. Outcomes

The primary outcome was therapeutic efficacy assessed using validated physician-reported scar severity scales. Secondary outcomes included patient-reported satisfaction, scar-type and skin type-specific responses, and safety outcomes.

2.4. Data Extraction and Synthesis

Study screening and selection were performed in Covidence [19]. Two independent reviewers conducted screening and data extraction, with conflicts resolved by consensus. Extracted data items were study design and setting, sample size (enrolled and analyzed), participant age and sex, Fitzpatrick phototype, scar morphology, insulin preparation and dose, delivery modality, treatment interval and number of sessions, follow-up duration, physician-rated scar severity scales and scores, patient-reported satisfaction, and adverse events. Because the included studies applied eight different scar-grading instruments, a range of insulin doses, and three different procedural platforms, clinical and methodological heterogeneity precluded meta-analysis. The synthesis is therefore narrative, grouped by comparator: for each comparison, the direction and magnitude of the reported between-group effect are presented together with the authors' reported test statistic.

The quality of the studies was determined using the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5 [20]. Risk of Bias (RoB) 2 was applied to the RCTs [21], while ROBINS-I V2 was applied to non-RCTs [22]. Two independent reviewers evaluated each study, with conflicts resolved by consensus (Supplementary Material S4).

3. Results

A total of 572 records were retrieved by the updated search (PubMed 302, Google Scholar 148, Scopus 61, CENTRAL 46, Embase 15; S2). After the removal of 62 duplicates, 510 records were screened by title and abstract, and 488 were excluded. Twenty-two reports were sought for retrieval, of which two could not be obtained, leaving 20 reports assessed for eligibility at full text. Six reports were excluded at full text, five due to incorrect study design and one due to wrong intervention, leaving 14 studies that met the eligibility criteria (Figure 3); no report was excluded on the basis of its results.

3.1. Demographics, Patient Characteristics, and Study Design

Of the 14 studies (Table 1), four were conducted in Egypt [23–26], three in Pakistan [27–29], three in India [30–32], and a single study in Thailand [33], Iran [34], Syria [7], and China [35]. The cohort comprised seven RCTs (four split-face) [23,24,27,32–35] and seven non-randomized comparative studies, of which six were split-face studies [25,26,28–31], and one was a prospective parallel-group study [7]. A total of 619 participants were included across all investigations, with sample sizes ranging from 16 [31] to 120 [7]. Since 10 of the 14 studies employed split-face designs, each participant received both the intervention and the comparator, one on each side of the face. The two sides of the same face are paired, within-person observations and cannot be treated as independent; the participant is therefore the unit of analysis, and between-side comparisons require paired methods. The original analyses of the 10 split-face studies accounted for this inconsistently: three used methods that account for pairing (paired tests [23,29] or a linear mixed-effects model [33]), four compared the sides with tests for independent samples [24,30,31,34], and

three did not state the test used for the between-side comparison [25,26,28]. As this review did not re-analyze individual-level data, between-side p -values from these studies should be interpreted with caution. Acne scar types were reported in five studies [7,24,25,28,32], and the Fitzpatrick skin type was reported in 9/14 studies, mostly types III–IV. All studies evaluated topical insulin as monotherapy or adjunctive therapy; doses ranged from 10 IU [25,32] to 40–50 IU [29,34], with breaks of 3–4 weeks and time spans varying from 9 weeks [23] to 12 months [7]. All studies utilized regular human insulin; however, the concentration, volume applied, and treated surface area were reported inconsistently, and only a few studies mentioned the timing of application relative to the procedure, making the derivation of a standardized dose impossible.

Post Acne Scars and Topical Insulin

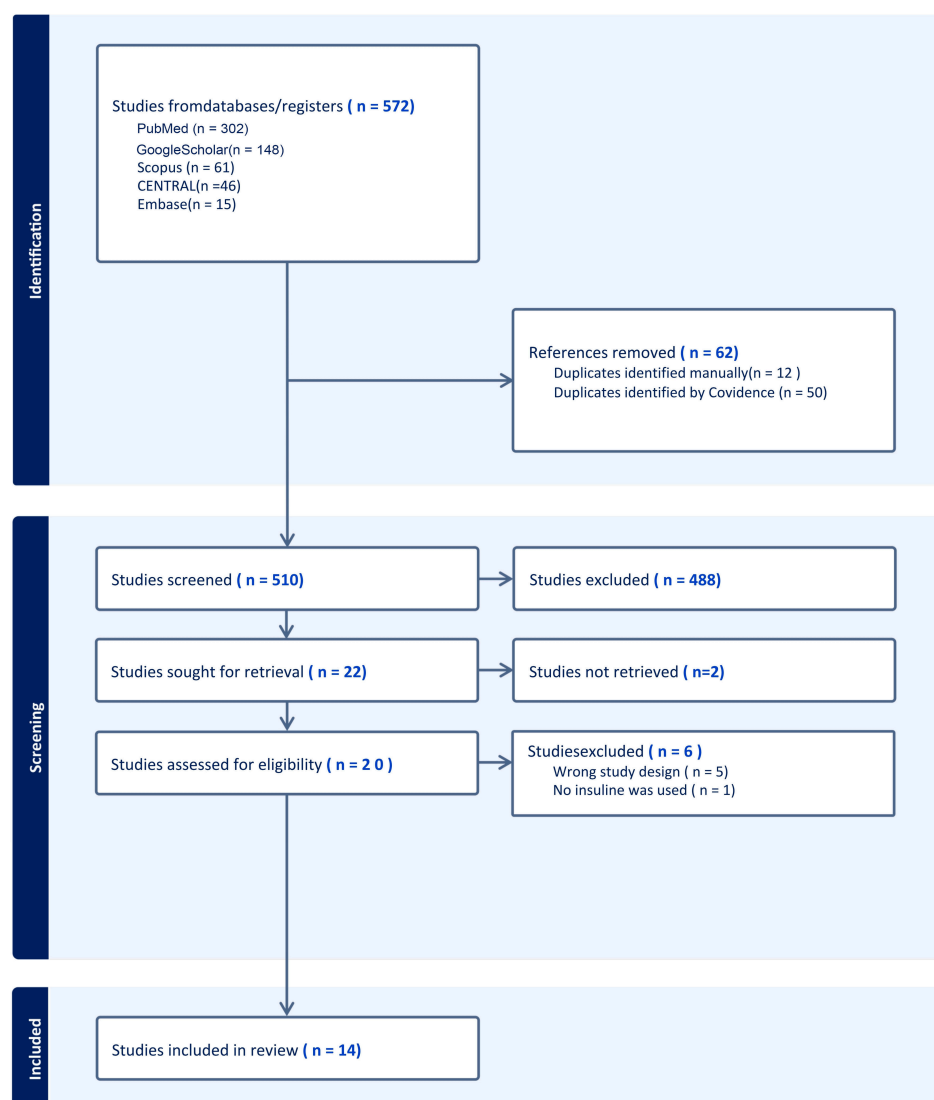


Figure 3. PRISMA 2020 flow diagram illustrating the study selection process.

Table 1. An overview of included studies and their characteristics.

Study (Year)	Design; Country	N enrolled (Withdrawals)	Arms	Age, Mean ± SD (Years); Female	Scar Types	Fitzpatrick Skin Type	Dose	Interval; Duration
Randomized controlled trials								
Abdelhay et al. (2025) [23]	RCT, split-face; Egypt	21 (0)	Side A: Actrapid insulin Side B: normal saline	29.5 ± 9.0; 76.2%	NR	III 33.3%; IV 66.7%	1–2 mL	Every 3 weeks; 9 weeks
Gahlot and Hussain (2025) [32]	RCT, parallel; India	50, 25 per arm (0)	Group 1: MN + regular human insulin Group 2: MN + autologous PRP	NR (range 18–35); NR	Rolling, boxcar, and deep ice pick (not quantified)	NR	10 U regular insulin	Every 3 weeks; 12 weeks (4 sessions)
Mubeen et al. (2023) [27]	RCT, parallel; Pakistan	80, 40 per arm (0)	Group A: topical insulin Group B: PRP	NR; 71.25%	NR	NR	2 mL	Every 4 weeks; 4 months
Peng et al. (2026) [35]	RCT, four parallel arms; China	52, 13 per arm (0)	MN; MN + insulin; MN + bFGF; MN + rh-aFGF	26.65 ± 0.629; 59.6%	NR	III 23.1%; IV 76.9%	1 mL insulin, topical	Monthly; 3 sessions, 3-month follow-up
Rageh et al. (2025) [24]	RCT, split-face; Egypt	30 (0)	Side A: fractional CO ₂ laser with topical insulin Side B: fractional CO ₂ laser with PRP	25.7 ± 4.6; 63.3%	Rolling 66.7%; ice pick 20.0%; boxcar 13.3%	III 66.6%; IV 26.7%; V 6.7%	0.5–1 mL	Every 4 weeks; 4 months
Rattananukrom et al. (2025) [33]	RCT, split-face; Thailand	30 (1: non-compliance with follow-up protocol)	Side A: Human Actrapid insulin Side B: normal saline (placebo)	30.66 ± 6.74; 55.17%	NR	III 37.93%; IV 62.07%	2 mL	Every 4 weeks; 4 months
Saki et al. (2025) [34]	RCT, split-face; Iran	30 (2: non-adherence to treatment protocol)	A: distilled water (placebo) B1: ophthalmic timolol maleate B2: topical regular insulin	32.2 ± 4.4; 66.7%	NR	II 10.0%; III 83.3%; IV 6.7%	50 units	Every 3 weeks; 9 weeks
Non-randomized comparative studies								
Abbas et al. (2022) [25]	Split-face; Egypt	30 (0)	Left side: Human Actrapid insulin Right side: vitamin C serum	26.73 ± 4.76; 76.7%	Boxcar 40.0%; ice pick 26.7%; rolling 26.7%; mixed 6.6%	NR	0.1 mL (100 IU/mL, 10 units)	Every 4 weeks; 4 months
Ali et al. (2024) [28]	Split-face; Pakistan	30 (0)	Human Actrapid insulin Contralateral side: MN alone	29.47 ± 8.36; 60%	Ice pick 60%; boxcar 20%; rolling 13.4%; mixed 6.6%	IV–VI (distribution not specified)	NR	Every 4 weeks; 4 months

Table 1. Cont.

Study (Year)	Design; Country	N enrolled (Withdrawals)	Arms	Age, Mean ± SD (Years); Female	Scar Types	Fitzpatrick Skin Type	Dose	Interval; Duration
Karkour et al. (2025) [7]	Prospective cohort, parallel groups; Syria	120: 1A 100, 1B 20 (2: missing sample at 12-month follow-up)	Group 1A: human Actrapid insulin (100 IU/mL) Group 1B: saline (placebo)	1A: 26.13 ± 6.12; 1B: 25.41 ± 5.22; 78.3%	1A: rolling 60.0%, boxcar 33.0%, ice pick 7.0% 1B: rolling 55.0%, boxcar 35.0%, ice pick 10.0%	II 16.7%; III 62.5%; IV 20.8%	40 units	Every 4 weeks; 12 months
Malik et al. (2024) [29]	Split-face; Pakistan	50 (0)	Right side: Humulin R Left side: MN alone	27.94 ± 5.06; 42%	NR	II 6%; III 44%; IV 50%	40 units	Every 4 weeks; 3 months
Mohamed et al. (2024) [26]	Split-face; Egypt	30 (0)	Side A: topical insulin Side B: hyaluronic acid	30.63 ± 4.72; 70.0%	NR	III 26.7%; IV 73.3%	1–2 mL	Every 3 weeks; 3.5 months
Mohta et al. (2024) [30]	Split-face; India	50 (0)	Side A: Human Actrapid insulin Side B: PRP	NR; NR	NR	NR	1–2 mL	Every 4 weeks; 5 months
Pawar et al. (2022) [31]	Simultaneous split-face; India	16 (2: non-adherence to treatment protocol)	Right side: Human Actrapid insulin, 40 IU/L solution Left side: PRP	24.96 ± 10.3; 56.25%	NR	NR	1–2 mL	Every 4 weeks; 4 months

Footnote: One row is shown per study. N is the number of participants enrolled, with withdrawals and their reasons in parentheses; in split-face studies, each participant received both treatments. Female is the percentage of female participants. Abbreviations: bFGF = bovine basic fibroblast growth factor; MN = microneedling; NR = not reported; PRP = platelet-rich plasma; RCT = randomized controlled trial; rh-aFGF = recombinant human acidic fibroblast growth factor; SD = standard deviation; U = units.

3.2. Risk of Bias in Included Studies

For RCTs: 3 out of 7 (42.9%) were judged to have an overall low risk of bias [23,33,34]. Rageh et al. (2025) [24], Gahlot and Hussain (2025) [32], and Peng et al. (2026) [35] had some concerns, while Mubeen et al. (2023) [27] was at high risk due to outcome measurement. The most common concern was selection of the reported result, affecting 4/7 RCTs [24,27,32,35], followed by measurement of the outcome, affecting 3/7 RCTs [27,32,35] (Figure 4).

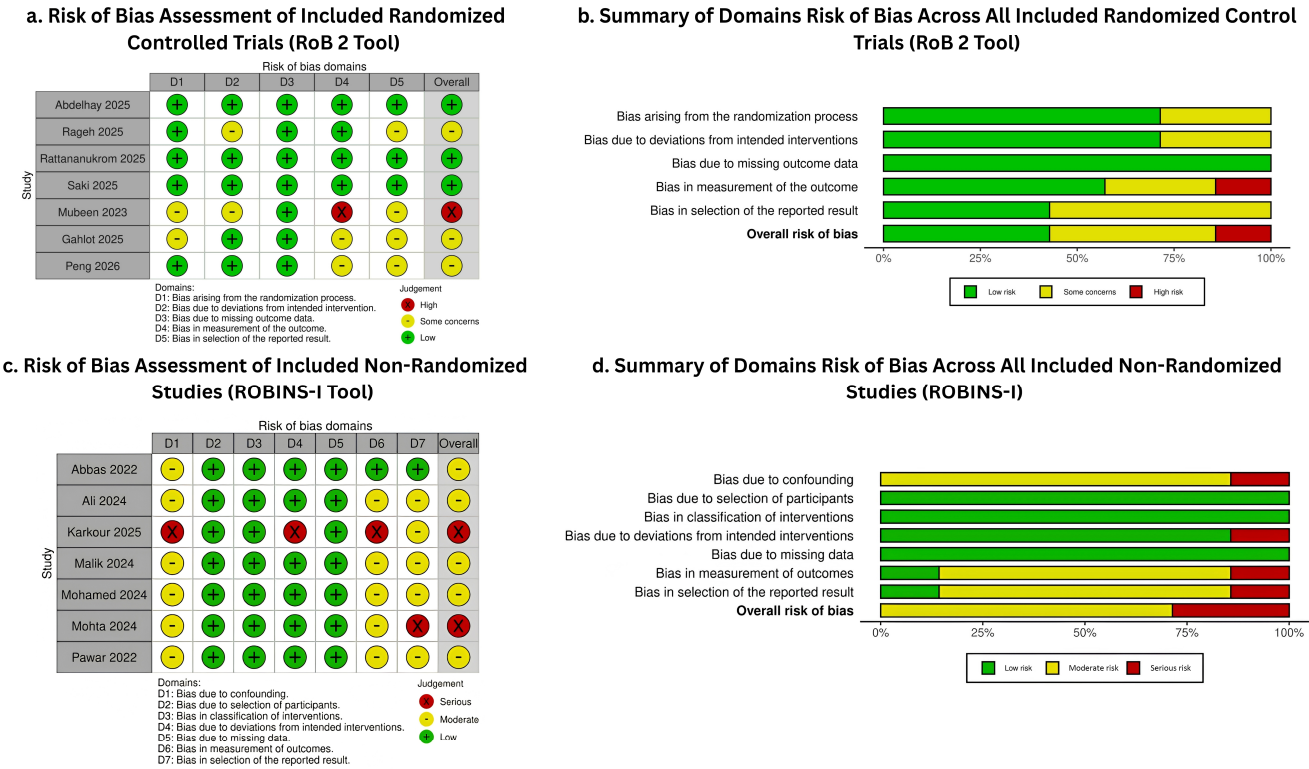


Table 2. Summary of study outcomes, efficacy, and significance.

Study (Year)	Design (N)	Insulin Arm	Comparator	Outcome Scale(s)	Result: Insulin vs. Comparator	Between-Group <i>p</i>	Direction
Insulin vs. placebo or procedure alone							
Abdelhay et al. (2025) [23]	RCT, split-face (21)	MN + insulin	MN + saline (placebo)	GS GS % improvement Lipper and Perez % improvement	35.8 ± 25.2% vs. 32.7 ± 19.4% 35.8 ± 17.8% vs. 33.6 ± 16.3%	0.518 0.543	NS
Rattananukrom et al. (2025) [33]	RCT, split-face (29 analyzed)	MFR + insulin	MFR + saline (placebo)	ECCA % reduction	46.77 ± 21.33% vs. 46.39 ± 20.14%	0.728	NS
Peng et al. (2026) [35]	RCT, parallel (52; 13 per arm)	MN + insulin	MN alone (other arms: MN + bFGF, MN + rh-aFGF)	ORR VISIA texture score change	69.23% vs. 46.15% 3.77 ± 1.25 vs. 2.23 ± 1.097	0.287 0.020	NS (ORR); favors insulin (texture)
Malik et al. (2024) [29]	Non-randomized, split-face (50)	MN + insulin	MN alone	GBQGS mean score, baseline → end	20.44 ± 3.54 → 9.78 ± 2.88 (Δ10.66) vs. 20.62 ± 3.23 → 10.54 ± 2.27 (Δ10.08)	NS	NS; shorter healing time and better tolerability with insulin
Ali et al. (2024) [28]	Non-randomized, split-face (30)	MN + insulin	MN alone	Modified ASAS, % improvement grade	Grade 3 (50–75%): 63.3% vs. 0%; grade 2: 36.7% vs. 0%; grade 1: 0% vs. 33.3%; grade 0: 0% vs. 66.7%	<0.001	Favors insulin
Karkour et al. (2025) [7]	Non-randomized, parallel (120; 100 vs. 20)	MN + insulin	MN + saline (placebo)	Goodman and Baron, qualitative response	Good: 50% vs. 25%; average: 40% vs. 50%; poor: 10% vs. 25%	0.001	Favors insulin
Insulin vs. platelet-rich plasma							
Gahlot and Hussain (2025) [32]	RCT, parallel (50; 25 per arm)	MN + insulin	MN + PRP	ASAS % reduction SQGS >75% improvement	41.10 ± 11.86% vs. 25.32 ± 9.72% 36% vs. 8%	0.015 0.023	Favors insulin
Mubeen et al. (2023) [27]	RCT, parallel (80; 40 per arm)	MN + insulin	MN + PRP	Goodman and Baron, qualitative: % reduction; improvement category	55.4 ± 12.7% vs. 23.3 ± 16.8% Marked: 50% vs. 0%; moderate: 50% vs. 67.5%; mild: 0% vs. 32.5%	0.001	Favors insulin
Rageh et al. (2025) [24]	RCT, split-face (30)	FCL + insulin	FCL + PRP	ASAS grade change	Both improved (within-group $\chi^2 = 34.1$ vs. 37.8); between-group $\chi^2 = 1.02$	0.794	NS
Mohta et al. (2024) [30]	Non-randomized, split-face (50)	MN + insulin	MN + PRP	Global Acne Scarring System, % improvement	52% vs. 28%	Not reported	Similar improvement (as stated by the authors)

Table 2. Cont.

Study (Year)	Design (N)	Insulin Arm	Comparator	Outcome Scale(s)	Result: Insulin vs. Comparator	Between-Group <i>p</i>	Direction
Pawar et al. (2022) [31]	Non-randomized, split-face (16; 14 analyzed)	MN + insulin	MN + PRP	Global Acne Scarring System, % improvement	45% vs. 26%	0.26	NS
Insulin vs. other active comparators							
Abbas et al. (2022) [25]	Non-randomized, split-face (30)	MN + insulin	MN + vitamin C	ASAS mean change SQGS	3.03 ± 0.82 vs. 2.93 ± 0.62 Higher with vitamin C (test statistic 15.62)	NS 0.0036	NS (ASAS); favors vitamin C (SQGS)
Mohamed et al. (2024) [26]	Non-randomized, split-face (30)	MN + insulin	MN + HA	GBQGS % improvement	49.2% vs. 47.7%	0.348	NS
Saki et al. (2025) [34]	RCT, split-face (30)	FCL + insulin	FCL + timolol; FCL alone	SCAR-S, ASAS, GBQGS mean change	SCAR-S: 1.27 ± 0.458 vs. 1.33 ± 0.900 vs. 1.13 ± 0.571 ASAS: 1.33 ± 0.488 vs. 1.27 ± 0.594 vs. 1.30 ± 0.535 GBQGS: 5.07 ± 2.939 vs. 5.33 ± 3.539 vs. 4.63 ± 2.251	0.728 0.970 0.879	NS

Footnote: Studies are grouped by comparator. Within-group improvement from baseline was statistically significant (*p* < 0.05) in every insulin arm and is not repeated in the table. Results are given as insulin vs. comparator. Direction refers to the between-group comparison only; NS indicates no statistically significant difference, which does not imply equivalence. Abbreviations: ASAS = Acne Scar Assessment Scale; bFGF = bovine basic fibroblast growth factor; ECCA = Échelle d’Évaluation Clinique des Cicatrices d’Acné; FCL = fractional CO₂ laser; GBQGS = Goodman and Baron Quantitative Global Scarring Scale; GSGS = Goodman and Baron Qualitative Global Scarring Scale; HA = hyaluronic acid; MFR = microneedle fractional radiofrequency; MN = microneedling; ORR = overall response rate; PRP = platelet-rich plasma; rh-aFGF = recombinant human acidic fibroblast growth factor; SCAR-S = Scar Global Assessment Scale; SQGS = Scar Quantitative Grading Scale.

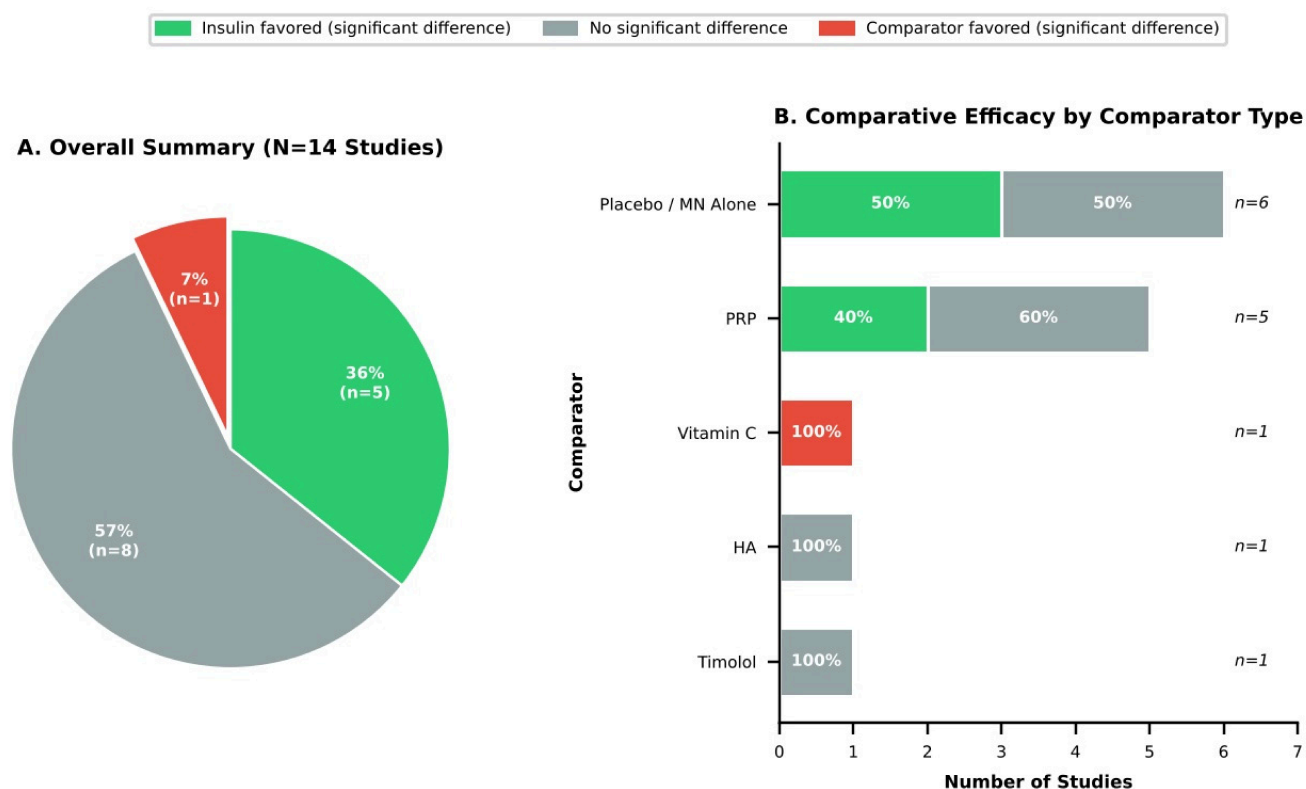


Figure 5. Comparative efficacy of insulin vs. other treatments for acne scarring. Footnote: Abbas et al. (2022) [25] was classified as favoring the comparator despite significant within-group improvement in both arms, as it is the only included study in which a comparator (Vitamin C) significantly outperformed insulin on any efficacy measure (SQGS, $p = 0.0036$); on ASAS, the two arms did not differ significantly. Mohta et al. (2024) [30] is shown with the studies reporting no significant difference only because the authors described similar improvement on both sides; as no between-group p -value was reported, its statistical significance could not be determined, while Peng et al. (2026) [35] is classified as favoring insulin due to a significant between-group difference in VISIA texture score, even though the overall response rate did not differ. “No significant difference” denotes the absence of a statistically significant between-group difference and does not imply equivalence.

3.3.1. Efficacy: Consistency of Baseline Improvement

Across procedural platforms (MN [$n = 11$], fractional CO₂ [$n = 2$], radiofrequency [$n = 1$]), different comparators, and different grading measures, all 14 investigations demonstrated a substantial improvement from baseline ($p < 0.05$). The range of improvement was $35.8 \pm 25.2\%$ [23] to $55.4 \pm 12.7\%$ [27]. Regarding categorical outcomes, 50% of patients in Mubeen et al.’s research (2023) [27] improved significantly ($>50\%$), and 63.3% of patients in Ali et al.’s research (2024) [28] achieved Grade 3 improvement (50–75%). These findings are in line with those from Karkour et al.’s study (2025) [7], where 50% of insulin-treated patients demonstrated a “good response” on the qualitative Goodman and Baron scale (Table 2). However, because insulin was always combined with a procedure and the comparator arms improved to a similar extent in most studies (Table 2), improvement from baseline reflects the combined treatment and cannot by itself be attributed to insulin; evidence for an insulin-specific effect rests on the between-group comparisons below (Sections 3.3.2–3.3.4).

3.3.2. Insulin vs. Placebo or MN Alone

Six studies compared insulin with placebo or microneedling alone. In four of these, the between-group difference was small and not statistically distinguishable [23,29,33,35].

In Malik et al. (2024) [29], both groups reduced quantitative Goodman and Baron scores by ~10 points, though insulin demonstrated shorter skin-healing time and better tolerability. Two non-randomized studies reported a between-group difference favoring insulin, at moderate [28] and serious [7] risk of bias, respectively: Ali et al. (2024) [28] found 63.3% of the insulin group achieved Grade 3 improvement (50–75%) vs. 66.7% of the MN-alone group showing no improvement ($p < 0.001$), and Karkour et al. (2025) [7] found 50% good response with insulin vs. 25% with placebo ($p = 0.001$) (Table 2). Peng et al. (2026) [35] found no significant difference in overall response rate between microneedling with insulin and microneedling alone (69.23% vs. 46.15%, $p = 0.287$), although the VISIA texture score improved significantly more with insulin (3.77 ± 1.25 vs. 2.23 ± 1.097 , $p = 0.020$).

3.3.3. Insulin vs. Platelet-Rich Plasma (PRP)

Five studies compared insulin with PRP. Two reported a statistically significant between-group difference favoring insulin [27,32], one at high risk of bias [27] and one with some concerns [32]. Mubeen et al. (2023) [27] showed $55.4 \pm 12.7\%$ vs. $23.3 \pm 16.8\%$ reduction in scar severity ($p = 0.001$), with 50% of insulin patients achieving ‘marked’ improvement vs. 0% in the PRP group. Of the remaining three studies, two reported no significant between-group difference [24,31]; Mohta et al. (2024) [30] reported greater mean improvement with insulin (52% vs. 28%), but stated only that an unpaired comparison showed similar improvement on both sides, without reporting a between-group p -value, so the statistical significance of this comparison could not be determined. Pawar et al. (2022) [31] found no significant difference between insulin plus MN (45%) and PRP plus MN (26%), and Rageh et al. (2025) [24] found no significant intergroup difference ($p = 0.794$), though both treatments considerably reduced scarring (Table 2). Gahlot and Hussain (2025) [32] reported a significantly greater ASAS reduction with insulin than PRP ($41.10 \pm 11.86\%$ vs. $25.32 \pm 9.72\%$, $p = 0.015$), with >75% improvement on the SQGS in 36% vs. 8% of patients ($p = 0.023$).

3.3.4. Insulin vs. Other Active Comparators

Abbas et al. (2022) [25] found no significant difference between insulin and vitamin C on the ASAS, though vitamin C performed somewhat better on the SQGS (15.62 vs. 12.78, $p = 0.0036$), the only study showing comparator superiority. Mohamed et al. (2024) [26] found no significant difference between insulin (49.2% improvement) and hyaluronic acid (47.7%) with MN ($p = 0.348$). Saki et al. (2025) [34] found no significant differences between insulin plus laser, timolol plus laser, and laser alone at all scales ($p > 0.05$) (Table 2).

3.4. Outcomes by Scar Type and Skin Type

Rolling and boxcar scars seem to respond the most (Table 3). Mubeen et al. (2023) [27] demonstrated that 75% of patients with rolling scars exhibited significant improvement ($p = 0.018$), and both boxcar and ice pick scars displayed notable improvement (~50% significant). Mohamed et al. (2024) [26] demonstrated that there was no significant difference in % improvement for rolling ($p = 0.250$), boxcar ($p = 0.992$), or ice pick ($p = 0.774$) scars compared to hyaluronic acid. Pawar et al. (2022) [31] discovered that although quantitative assessments showed no differences in boxcar scars between groups, qualitative GAS significantly preferred insulin ($p = 0.008$). Gahlot and Hussain (2025) [32] similarly found a more favorable reaction in rolling and boxcar scars with insulin, whereas deep ice pick scars showed slight improvement in both categories.

Table 3. Effect of topical insulin on atrophic acne scar outcomes according to scar morphology and the Fitzpatrick skin type: summary of evidence across included studies.

Study (Year)	Factor	Outcome Measured/Scale Used	Categories	Numerical Key Findings—Insulin Arm	Comparator—Numerical	Statistical Significance
Mohamed et al. (2024) [26]	Scar type	% improvement	Boxcar	54.87 ± 5.20%	54.80 ± 16.11%	Between insulin vs. HA: $p = 0.992$ (NS)
			Ice pick	37.06 ± 7.81%	34.44 ± 12.51%	$p = 0.774$ (NS)
			Rolling	60.63 ± 9.66%	50.26 ± 13.13%	$p = 0.250$ (NS)
			Mixed	46.10 ± 14.51%	46.47 ± 14.78%	$p = 0.944$ (NS)
Mohta et al. (2024) [30]	Scar type	Clinical scar grading	N/A	Greater improvement in boxcar and ice pick scars (Numerical values not reported)	Control arm (Numerical data not reported)	NS
Mubeen et al. (2023) [27]	Scar type	Goodman and Baron score percentage improvement	Ice pick	Marked (>50%): 50% Moderate (25–50%): 50%	Moderate (25–50%): 60% Mild (<25%): 40%	$p = 0.019$ (S) Additional: (Scar duration <3 years related to better response)
			Boxcar	Marked (>50%): 47.1% Moderate (25–50%): 52.9%	Moderate (25–50%): 63.3% Mild (<25%): 36.7%	$p = 0.001$
			Rolling	Marked (>50%): 75% Moderate (25–50%): 25%	Moderate (25–50%): 100%	$p = 0.018$
	Skin type: Fitzpatrick skin	Fitzpatrick skin type percentage improvement	Type IV:	Marked (>50%): 54.3% Moderate (25–50%): 45.7%	Moderate (25–50%): 69.4% Mild (<25%): 30.6%	$p = 0.001$
			Type V:	Marked (>50%): 25% Moderate (25–50%): 75%	Moderate (25–50%): 66.7% Mild (<25%): 33.3%	$p = 0.350$
			Type VI:	Moderate (25–50%): 100%	Mild (<25%): 100%	$p = 0.157$
Pawar et al. (2022) [31]	Scar type	% improvement	Ice pick	Ice pick: 42.24%	PRP: Ice pick: 39.67%	Ice pick: $p = 0.88$ (NS)
			Boxcar	51.20%	24.74%	Boxcar: $p = 0.66$ (NS) Note: Boxcar scars: significant post-treatment GAS difference (insulin 5.58 ± 2.91 vs. PRP 9.42 ± 3.21 ; $p = 0.008$) (S).
			Rolling	22.92%	23.56%	Rolling: $p = 0.97$ (NS)
Gahlot and hussain (2025) [32]	Scar morphology	ASAS/SQGS subgroup analysis	Rolling, boxcar, deep ice pick	Better therapeutic response in rolling and boxcar scars with insulin	PRP: deep ice pick scars showed minimal improvement in both arms	Reported qualitatively (no subgroup p -value)

Table 3. Cont.

Study (Year)	Factor	Outcome Measured/Scale Used	Categories	Numerical Key Findings—Insulin Arm	Comparator—Numerical	Statistical Significance
Rageh et al. (2025) [24]	Scar type	ASAS (after)	Rolling	Very Mild: 10% Mild: 60% Moderate: 30% Severe: 0%	Very Mild: 15% Mild: 60% Moderate: 25% Severe: 0%	I: F = 6.6, $p = 0.351$ (NS) C: F = 1.25, $p = 0.9$ (NS)
			Boxcar	Very Mild: 0% Mild: 50% Moderate: 25% Severe: 25%	Very Mild: 0% Mild: 75% Moderate: 25% Severe: 0%	
			Ice pick	Very Mild: 33.3% Mild: 50% Moderate: 16.7% Severe: 0%	Very Mild: 16.7% Mild: 50% Moderate: 33.3% Severe: 0%	
	Scar type	Satisfaction (%)	Rolling	69.5 ± 9.7	71.5 ± 9.4	I: $p = 0.046$ (S) F = 3.46 C: $p = 0.089$ (NS) F = 2.6
			Boxcar	66.2 ± 7.5	72.5 ± 9.5	
			Ice pick	58.3 ± 7.5	61.6 ± 9.8	
Karkour et al. (2025) [7]	Skin type	Percentage improvement	90% of PIH cases occurred in Fitzpatrick III. 10% of PIH cases occurred in Fitzpatrick IV.			$p = 0.003$ (S)
Saki et al. (2025) [34]	Skin type	SCAR-S	Fitzpatrick II: 1.33 ± 0.52 Fitzpatrick III: 1.18 ± 0.63 Fitzpatrick IV: 1.50 ± 1.00			$p = 0.747$
		ASAS	Fitzpatrick II: 1.00 ± 0.89 Fitzpatrick III: 1.32 ± 0.47 Fitzpatrick IV: 1.50 ± 0.58			$p = 0.455$
		GBQGS	Fitzpatrick II: 4.17 ± 4.07 Fitzpatrick III: 4.82 ± 2.56 Fitzpatrick IV: 7.25 ± 2.50			$p = 0.162$
		DLQI	Fitzpatrick II: 5.00 ± 2.366 Fitzpatrick III: 2.00 ± 1.245 Fitzpatrick IV: 3.00 ± 0.000			$p = 0.009$ Greater difference in Fitzpatrick II.

Footnote: ASAS refers to the Acne Scar Assessment Scale; GAS refers to the Global Assessment Score; GBQGS indicates the Goodman and Baron Quantitative Global Scarring Scale; SCAR-S denotes the Scar Global Assessment Scale; and DLQI represents the Dermatology Life Quality Index. PRP indicates platelet-rich plasma, HA indicates hyaluronic acid, and PIH refers to post-inflammatory hyperpigmentation. Clinical improvement categories were defined as marked improvement (>50%), moderate improvement (25–50%), and mild improvement (<25%). The Fitzpatrick skin type represents the dermatologic classification of skin phototypes according to pigmentation and ultraviolet radiation response. Values are reported as mean ± standard deviation (SD) or as percentage distribution of patients within improvement categories, as presented in the original studies. S indicates a statistically significant difference ($p < 0.05$), while NS indicates no statistically significant difference ($p \geq 0.05$). When numerical data were not available, findings were summarized qualitatively according to the authors' reported outcomes.

Ice pick scars showed the least responsiveness. Three studies indicated no major advantage compared to comparators (hyaluronic acid $p = 0.774$ [26], PRP $p = 0.88$ [31], PRP $p = 0.9$ [24]), while only Mubeen et al. (2023) [27] noted a significant result ($p = 0.019$), contradicting the other findings and originating from a study with a high risk of bias. According to Mubeen et al. (2023) [27], insulin was effective solely for Fitzpatrick skin type IV ($p = 0.001$) and exhibited no significant improvement in types V or VI. Saki et al. (2025) [34] discovered that only patients with Type II skin showed a notable enhancement in DLQI ($p = 0.009$). Karkour et al. (2025) [7] discovered that 90% of PIH cases were in Type III skin ($p = 0.003$) (Table 3).

3.5. Patient-Reported Outcomes and Satisfaction

Eight studies indicated satisfaction results; all demonstrated improvement, with four showing no significant statistical difference between insulin and the comparator [24,26,33,34]. Malik et al. (2024) [29] and Karkour et al. (2025) [7] demonstrated a notable difference that favored insulin. The only exception was Abbas et al.'s research (2022) [25], in which vitamin C was considerably favored (excellent response: 6.7% vs. 46.7%, $p < 0.001$). Rattananukrom et al. (2025) [33] found overall high scores (patient satisfaction 8.05 ± 1.80 ; self-perceived improvement 7.30 ± 1.50) with no significant differences among groups ($p = 0.944$) (Table 4). Gahlot and Hussain (2025) [32] found an 'excellent' satisfaction level in 48% of insulin-treated individuals compared to 8% in those receiving PRP ($p = 0.0008$).

3.6. Side Effects and Adverse Effects

Topical insulin was generally well accepted in all studies, with no serious or lasting side effects. The most frequently observed side effect was temporary erythema, affecting nearly all patients [7,25], which typically resolved on the day of the procedure or the next day in most studies; Rageh et al. (2025) [24] found an average resolution time of 5.8–6.8 days. Malik et al. (2024) [29] demonstrated reduced average erythema scores when insulin was used compared to MN alone (1.82 ± 0.62 vs. 2.92 ± 1.08 , $p = 0.009$). Temporary mild discomfort was noted in 10 studies (10–90% of patients). Gahlot and Hussain (2025) [32] observed erythema and edema in 8% of insulin-treated patients compared to 12% for PRP, while Peng et al. (2026) [35] noted erythema, edema, burning, and pain in every patient, with resolution occurring within 3 days to 2 weeks.

PIH was reported in 6 studies, occurring in 0–20.2% with no statistical significance; 90% of PIH cases in Karkour et al. (2025) [7] were in Fitzpatrick III ($p = 0.003$). Hypoglycemia symptoms were observed in 5 of the 119 insulin-treated patients in a trial (Karkour et al. (2025) [7]; 4.2% vs. 0% in the control group, $p = 0.31$), but none resulted in any complications or permanent effects; the symptoms were confirmed by a serum glucose measurement in that trial, and only a few studies reported monitoring blood glucose levels. In that study, adverse events were reported for the full cohort of 158 participants with different atrophic scar types (119 insulin, 39 control), rather than for the acne-scar subgroup of 120 participants included in Tables 1 and 2; these events, including the hypoglycemia-related symptoms, therefore cannot be attributed specifically to patients with acne scars. No other systemic events were reported (Table 5).

Table 4. An overview of qualitative key findings of intervention and comparators, and their statistical significance.

Study (Year)	Scale	Key Findings—Insulin Arm	Key Findings—Comparator	Statistical Significance
Abbas et al. (2022) [25]	4-point Likert	Poor: 9 (30.0%) Fair: 15 (50.0%) Good: 4 (13.3%) Excellent: 2 (6.7%)	Vit C: Poor: 3 (10.0%) Fair: 5 (16.7%) Good: 8 (26.7%) Excellent: 14 (46.7%)	$p < 0.001$ (S, favors Vitamin C)
Karkour et al. (2025) [7]	10-point subjective satisfaction scale	Good response: 40/100 (40%) Average response: 50/100 (50%) Poor response: 10/100 (10%)	Good response: 3/20 (15%) Average response: 12/20 (60%) Poor response: 5/20 (25%)	$p = 0.001$ (S, favors insulin)
Malik et al. (2024) [29]	10-point subjective satisfaction scale	Mean satisfaction score: 6.04 ± 1.70	MN alone: Mean satisfaction score: 5.56 ± 1.61	$p < 0.001$ (S; favors insulin)
Mohamed et al. (2024) [26]	Quartile satisfaction scale (Grade 0–3)	Grade 3: 14 patients Grade 2: 8 patients Grade 1: 4 patients Grade 0: 4 patients	HA: Grade 3: 12 patients Grade 2: 9 patients Grade 1: 4 patients Grade 0: 5 patients	$p = 0.616$ (NS)
Rattananukrom et al. (2025) [33]	VAS (0–10)	Self-rated scar improvement: 7.30 ± 1.50 Patient satisfaction: 8.05 ± 1.80	Self-rated scar improvement: 6.92 ± 1.50 Patient satisfaction: 8.09 ± 1.60	Improvement: $p = 0.37$ (NS) Satisfaction: $p = 0.944$ (NS)
Saki et al. (2025) [34]	DLQI	Mean DLQI: 3.80 ± 2.704 (Laser + Insulin)	Laser alone: 4.67 ± 3.284 Laser + Timolol: 5.53 ± 3.662	$p = 0.337$ (NS)
Gahlot and Hussain (2025) [32]	4-point Likert	Excellent: 12 (48%)	PRP: Excellent: 2 (8%)	$p = 0.0008$ (S, favors insulin)
Rageh et al. (2025) [24]	% satisfaction mean $\pm$ SD	$66.8 \pm 9.8\%$	FCL + PRP: 69.6 ± 10.1	T: 1.1
	% satisfaction range	50–90	50–80	$p = 0.672$ (NS)

Footnote: The table highlights the scale, key findings for both intervention and comparators, and any reported statistical significance. VAS refers to the Visual Analog Scale, and DLQI refers to the Dermatology Life Quality Index. Patient satisfaction was assessed using different validated instruments across studies, including 4-point Likert scales, 10-point subjective satisfaction scales, quartile satisfaction grading systems (Grade 0–3), and percentage-based satisfaction reporting. In the Likert scale, categories typically represent poor, fair, good, and excellent treatment satisfaction. VAS scores range from 0 to 10, with higher scores indicating greater perceived improvement or satisfaction. DLQI is a dermatology-specific quality-of-life instrument where lower scores indicate better quality of life. Results are presented either as the number of patients with percentage (%), mean $\pm$ standard deviation (SD), or score distribution across categories, according to the original study reports. S indicates a statistically significant difference ($p < 0.05$), while NS indicates no statistically significant difference ($p \geq 0.05$). When applicable, the direction of significance (favoring insulin or comparator treatment) is indicated based on the reported statistical comparison.

Table 5. A summary of reported adverse effects.

Study (Year)	Key Side Effects—Insulin Arm	Key Side Effects—Comparator	Significance
Abbas et al. (2022) [25]	Erythema: 2 (6.7%) Edema: 4 (13.3%) Infection: 4 (13.3%) Hyperpigmentation: 1 (3.3%) Pain: 3 (10.0%)	Vit C: Erythema: 2 (6.7%) Edema: 4 (13.3%) Infection: 4 (13.3%) Hyperpigmentation: 2 (6.7%) Pain: 2 (6.7%)	p -value = 0.97 Test significance: 0.53
Ali et al. (2024) [28]	One patient experienced transient erythema for roughly one week, which resolved naturally and did not recur since the physician used a gentler technique during the procedure. One patient reported mild pain during the procedure, which alleviated with the prolonged application of topical anesthetic.		N/A
Karkour et al. (2025) [7]	Dryness: 119 (100%) Temporary erythema: 119 (100%) Burning sensation: 109 (91.6%) Hyperpigmentation: 24 (20.2%) Infection: 11 (9.2%) Miliaria: 6 (5.0%) Bruises: 4 (3.4%) Induced acne: 5 (4.2%) Hypoglycemia-related symptoms: 5 (4.2%) Persistent erythema: 2 (1.7%)	Dryness: 39 (100%) Temporary erythema: 39 (100%) Burning sensation: 37 (94.9%) Hyperpigmentation: 5 (12.8%) Infection: 3 (7.7%) Miliaria: 2 (5.1%) Bruises: 1 (2.6%) Induced acne: 0 (0%) Hypoglycemia-related symptoms: 0 (0%) Persistent erythema: 0 (0%)	Dryness, temporary erythema, and burning sensation, $p = 0.49$ Hyperpigmentation $p = 0.19$ Infection $p = 0.35$ Miliaria $p = 0.97$ Induced acne $p = 0.31$ Hypoglycemia-related symptoms $p = 0.31$ Bruises $p = 0.77$ Persistent erythema $p = 0.55$ (all NS)
Malik et al. (2024) [29]	Peeling: 7.04 ± 0.75 Erythema: 1.82 ± 0.62 Swelling: 1.38 ± 0.53	MN alone: Peeling: 8.14 ± 1.01 Erythema: 2.92 ± 1.08 Swelling: 1.56 ± 0.61	Peeling $p = 0.103$ (NS) Erythema $p = 0.009$ (S) Swelling $p < 0.001$ (S)
Mohamed et al. (2024) [26]	All patients developed transient erythema the day following the surgery. One patient experienced PIH Pain levels varied from 2 to 6. No hypoglycemia cases were detected		N/A
Mohta et al. (2024) [30]	A minority of individuals experienced transient erythema, pain, and edema. No dyspigmentation or scarring was observed. No changes in blood glucose levels were noted.		N/A
Mubeen et al. (2023) [27]	Transient mild pain, erythema, and edema resolved within the same day in most patients. Zero PIH, scarring, or alterations in blood glucose levels were reported.		N/A
Pawar et al. (2022) [31]	Adverse effects were mild and transient. Erythema ($n = 8$), pain ($n = 6$), Edema ($n = 3$) Zero PIH, scarring, or alterations in blood glucose levels reported.		N/A
Rageh et al. (2025) [24]	Moderate pain (90% of cases). Erythema and edema were consistently observed and resolved within 6.8 ± 0.91 days on the insulin-treated side and 5.8 ± 0.91 days on the PRP-treated side. Zero PIH or other adverse effects were documented.		All outcomes: (NS) Downtime of erythema and edema by 1 day: $t = 4.2$, $p < 0.001$ (HS)

Table 5. Cont.

Study (Year)	Key Side Effects—Insulin Arm	Key Side Effects—Comparator	Significance
Rattananukrom et al. (2025) [33]	No hypoglycemic events. Transient procedure-related pain well tolerated; decreased with sessions. Post-MFR erythema, self-limited; resolved within days. PIH: 1 patient (bilateral)	NS	
Saki et al. (2025) [34]	No adverse events occurred on either placebo or intervention sides.	N/A	
Abdelhay et al. (2025) [23]	Edema most common SE Erythema second most common SE PIH: 2 patients (bilateral) Skin type/exposure: 1 Type IV (moderate sun), 1 Type III (high sun exposure)	N/A	
Gahlot and Hussain (2025) [32]	Erythema: 2 (8%) Edema: 2 (8%) PIH: 1 (4%) No serious complications reported	PRP: Erythema: 3 (12%), Edema: 3 (12%), PIH: 2 (8%). All effects mild and self-limiting	
Peng et al. (2026) [35]	Erythema, edema, burning sensation, and pain in all patients Exudation and scabbing in a small number Resolved within 3 days to 2 weeks	MN alone, MN + bFGF and MN + rh-aFGF: comparable profile. No infection, dyspigmentation, or secondary scarring in any group	

Footnote: The table highlights the reported adverse effects in both intervention and comparator groups, and their statistical significance. MN refers to microneedling, PRP refers to platelet-rich plasma, Vit C refers to topical vitamin C, and PIH indicates post-inflammatory hyperpigmentation. Adverse events reported across studies primarily included erythema, edema, pain, dryness, burning sensation, hyperpigmentation, infection, miliaria, bruising, and acneiform eruptions, most of which were mild and transient. Some studies reported outcomes as the number of affected patients (n, %), while others reported mean severity scores $\pm$ standard deviation (SD). Hypoglycemia-related symptoms refer to systemic symptoms potentially related to insulin exposure; these were reported in one study only [7], resolved with oral sugar intake, and were confirmed by serum glucose measurement in that study. Data for Karkour et al. (2025) [7] refer to the full study cohort ($n = 158$; 119 insulin, 39 control), which included atrophic scars other than acne scars, and not to the acne-scar subgroup ($n = 120$) shown in Tables 1 and 2. S indicates a statistically significant difference ($p < 0.05$), HS indicates highly significant ($p < 0.001$), and NS indicates no statistically significant difference ($p \geq 0.05$). When comparator data or statistical testing were not reported in the original study, this was indicated as not available (N/A).

4. Discussion

This review partially supports our hypothesis. Topical insulin appears to be a well-tolerated, low-cost adjuvant in the management of post-acne atrophic scars, although its efficacy beyond that of the accompanying procedure remains uncertain. Across the 14 studies, all showed significant clinical improvement from baseline, but because comparator arms usually improved to a similar degree, this largely reflects the accompanying procedure. Between-group results varied: a minority demonstrated notable superiority, particularly for rolling and boxcar scars, although none of those comparisons came from a study at low risk of bias; half found no statistically significant difference from well-established alternatives, mainly PRP, which does not establish equivalence; and only one study showed slightly less efficacy than vitamin C [25].

In comparisons of insulin to placebo, some research indicated no significant difference, potentially due to an improper technique or dosage, or the suggestion that microneedling might be the primary therapeutic mechanism. Contamination in split-face designs, where insulin given to one side might be absorbed systemically and influence the opposite control side, skewing split-face comparisons toward the null, is another reason specific to this body of evidence. Compared with PRP, which has an established advantage in wound healing and scar remodeling [36], insulin showed no significant difference in two of five studies, while one did not report a between-group *p*-value [30] and a significant advantage in two, one at high risk of bias and one with some concerns [27,32]. Thus, while topical insulin contributes to clinical improvement, its superiority over other adjuvant therapies remains uncertain. It was used in conjunction with adjuvant delivery methods, such as fractional CO₂, microneedling, or micro-fractional radiofrequency, in all included studies. These methods increase the effect through enhanced trans-epidermal delivery and synergistic remodeling [37,38].

Two systematic reviews that preceded ours successfully managed to combine data for the comparison of microneedling [16,17]. We have not combined data since the studies used for analysis used eight grading scales on three different procedural systems. The trade-off in this case is lower precision, and our findings should be viewed as indicative of this problem. Patient-related outcomes consistently revealed improvement and satisfaction; however, superiority to alternative methods has not been consistently shown. Outcome measures can be influenced by placebo effect, patient expectations [39,40], initial severity of scars [41], and previous treatment experience [42].

Most evidence showed that rolling and boxcar scars had the most consistent response, consistent with other microneedling studies. Rolling scars have a prominent fibrous component attaching the dermis to the underlying musculo-fascial layer [43]. Needle penetration disrupts these subdermal fibrotic strands and initiates a wound-healing cascade [44], potentiated by the healing effects of insulin. Boxcar scars, with their wide U-shaped base, may permit more localized insulin penetration to dermal fibroblasts, improving collagen remodeling [33,45]. In contrast, ice pick scars are deeper, narrower defects that often require more aggressive interventions such as punch excision or TCA CROSS [44,46]. Future studies should stratify by scar type to better assess insulin's role.

Topical insulin appeared well tolerated, as reported adverse effects were largely limited to temporary local reactions, usually pain and erythema caused by the method of administration. PIH occurred bilaterally in split-face trials and was more common among people with Type III skin. The only side effect of a systemic nature was hypoglycemia occurring in five participants of one trial, whose safety data also included patients with scars other than acne scars. Because blood glucose was monitored in only a few studies, systemic absorption and the risk of hypoglycemia cannot be excluded, and these safety findings should be regarded as provisional.

Topical insulin has a notable economic advantage. Indicative figures place the cost per session using regular human insulin (~40 units) at approximately \$25 [47], against \$500 to \$2500 per PRP treatment [48]. These are list estimates rather than the output of a costing study and exclude consumables, clinician time, and the number of sessions required, and no formal cost-effectiveness analysis of topical insulin for acne scarring has been published. Even allowing for this, the difference in order of magnitude suggests that insulin may be accessible in settings where PRP is not.

Topical insulin can serve as an adjunct or alternative when standard therapies are contraindicated (e.g., PRP in platelet dysfunction syndromes, critical thrombocytopenia, hemodynamic instability, or bloodstream infection) and in limited-resource settings. Further studies are needed to demonstrate its efficacy when combined with other treatments to achieve a synergistic effect.

The included studies were mostly of moderate quality, with high variability in design, comparators, and outcome measures, precluding meta-analysis. Only 7 of 14 studies were RCTs, and 71.4% of non-RCTs showed moderate bias. Our interpretation was therefore adjusted by risk-of-bias findings: because selective reporting affected 4 of 7 RCTs, outcome measurement 3 of 7 RCTs, and confounding all 7 non-RCTs, the apparent efficacy of topical insulin may have been overstated and was interpreted as suggestive rather than confirmatory. All three RCTs judged at low risk of bias found no significant difference between insulin and comparator, whereas no comparison favoring insulin arose from a study at low risk of bias. As a result, the three low-risk RCTs received more interpretive weight, and conclusions regarding superiority over PRP or vitamin C were purposefully framed as uncertain. Generalizability is limited by geographic concentration (Egypt, Pakistan, India) and dominance of Fitzpatrick skin types III–IV, although these phototypes account for most of the global population and bear a disproportionate scarring burden. Follow-up was short, ranging from 9 weeks to 12 months, with most studies not exceeding 6 months, and eight distinct scar scales were used. Ten of the 14 studies used split-face designs, whose paired structure was not consistently accounted for in the original analyses, and the small total number of patients means that the results cannot be considered conclusive. Eligibility was restricted to English-language publications, which may have excluded relevant evidence given the geographic distribution of the included studies. The lack of a consistent insulin dose (10–50 IU) limits standard protocol recommendations.

These results can be used as an evidence base from which future research can be developed. Large-scale, high-quality multicenter randomized controlled trials will have to be conducted with standard protocols and longer follow-ups. Future studies need to stratify based on scar type and also conduct dose-finding studies to identify the most appropriate concentrations and frequencies for the administration of insulin.

5. Conclusions

Clinical improvement of atrophic acne scars in relation to baseline was observed in all 14 studies reviewed here, irrespective of the mode of administration of insulin, although comparator arms improved similarly in most studies, so this improvement cannot be attributed to insulin alone. In three of the six studies comparing insulin with PRP or HA, insulin did not differ significantly from the comparator, and one further study reported no between-group *p*-value; this does not establish equivalence, and none of the studies reporting superiority were at low risk of bias. One study found vitamin C superior on one out of two assessment scales. Rolling and boxcar scars responded the most favorably, while ice pick scars responded poorly, as they do to most non-surgical options.

None of the 14 trials reported any serious adverse effects. Adverse events were predominantly transient and local; all patients experienced erythema after the procedure,

while some experienced mild pain or edema. However, a systemic event was also reported: in one trial, whose safety data also covered scars other than acne scars, five patients experienced temporary hypoglycemia symptoms that resolved with oral sugar intake, and since only a few trials measured glucose levels routinely, the systemic absorption rate is poorly defined.

The evidence has real gaps. Only 7 of the 14 studies were RCTs. Dosing varied from 10 to 50 IU with no protocol consensus. Most patients were Fitzpatrick III or IV from a small group of countries, and follow-up rarely went past six months. Insulin is not ruled out by this, but it does indicate that the hypothesis is currently based on a small number of studies, most of which are small; given the limited number of patients, the results cannot yet be considered certain, and larger studies are needed.

Overall, topical insulin is a promising adjunct to microneedling, fractional CO₂ laser, or radiofrequency, especially where PRP is unaffordable or not an option, but the evidence remains heterogeneous and limited by study design and risk of bias. The next step is multicenter RCTs with standardized dosing, longer follow-up periods, and stratification by scar type.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/cosmetics13060286/s1>. Supplementary Material S1: PRISMA 2020 checklist; Supplementary Material S2: Search strategy; Supplementary Material S3: PICO framework; Supplementary Material S4: Risk-of-bias assessment of studies evaluating topical insulin for atrophic acne scars.

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Abbreviations

The following abbreviations are used in this manuscript:

Akt	Protein Kinase B
ASAS	Acne Scar Assessment Scale
CENTRAL	Cochrane Central Register of Controlled Trials
DLQI	Dermatology Life Quality Index
ECCA	Échelle d'Évaluation Clinique des Cicatrices d'Acné
ECM	Extracellular Matrix
eNOS	Endothelial Nitric Oxide Synthase
ERK1/2	Extracellular Signal-Regulated Kinases 1/2
FCL	Fractional Carbon Dioxide Laser
FGF-R	Fibroblast Growth Factor Receptor
GAGs	Glycosaminoglycans
GAS	Global Assessment Score
GBQGS	Goodman and Baron Quantitative Global Scarring Scale
Grb2/SOS	Growth Factor Receptor-Bound Protein 2/Son of Sevenless
GS GS	Goodman and Baron Qualitative Global Scarring Scale
GSK-3 β	Glycogen Synthase Kinase 3 Beta
HA	Hyaluronic Acid
IR	Insulin Receptor
IRS	Insulin Receptor Substrates
IU	International Units
MEK	Mitogen-Activated Protein Kinase Kinase
MeSH	Medical Subject Headings
MFR	Microneedle Fractional Radiofrequency
MN	Microneedling
mTOR	Mammalian Target of Rapamycin
NO	Nitric Oxide
PI3K	Phosphoinositide 3-Kinase
PICO	Population, Intervention, Comparison, Outcome
PIH	Post-Inflammatory Hyperpigmentation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PRP	Platelet-Rich Plasma
PTP1B	Protein Tyrosine Phosphatase 1B
Raf	Rapidly Accelerated Fibrosarcoma
Ras	Rat Sarcoma
RCT	Randomized Controlled Trial
RoB 2	Risk of Bias 2 Tool
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
RTK	Receptor Tyrosine Kinase
SCAR-S	Scar Global Assessment Scale
SD	Standard Deviation
SQGS	Scar Quantitative Grading Scale
TCA CROSS	Trichloroacetic Acid Chemical Reconstruction of Skin Scars
TGF- β	Transforming Growth Factor Beta
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

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