Review Article

Topical Insulin for Neurotrophic-Related Epithelial Defects: Where do We Stand? A Systematic Review

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Abstract

Purpose: To review the existing literature to evaluate the utility of insulin eye drops as a treatment for neurotrophic-related epithelial defects.

Methods: A comprehensive literature search of Medline, Embase, and Web of Science and additional manual searches were conducted using relevant keywords. All articles published from January 2005 to January 2024 were examined. Studies on the use of topical insulin drops in neurotrophic epithelial defects were included.

Results: A total of 16 articles were found relevant to be discussed in the review. All included patients had neurotrophic-related epithelial defects ranging from 3.8 mm^2 to 144 mm^2. After treatment with topical insulin, most of the epithelial defects showed a complete epithelialization. Various concentrations and types of insulin were used. The studies also varied in the type of vehicle used in the preparation of insulin drops. Two randomized controlled trials demonstrated that topical insulin drops were more effective than conventional treatment with artificial tears or autologous serum. All included studies, except for two, reported the absence of local or systemic side effects.

Conclusions: Topical insulin is a promising and effective (adjuvant) treatment for neurotrophic keratopathy. It facilitates the healing of neurotrophic epithelial defects and offers many advantages over the current treatment options; insulin is widely available and it is relatively inexpensive. Topical insulin drops do not affect systemic blood glucose levels and are well tolerated. However, further investigation is needed.

Keywords: Corneal epithelial defects, Corneal ulcer, Eye drops, Keratopathy, Neurotrophic keratopathy, Neurotropic keratitis, Topical insulin

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Introduction

Neurotrophic keratopathy (NK) is a corneal condition characterized by a reduction (hypoesthesia) or loss (anesthesia) of corneal sensitivity due to a partial or total impairment of the trigeminal innervation.

The trigeminal ophthalmic branch has a motor arc that regulates blinking and an autonomic arc that stimulates tear secretion. Together, these two arcs provide protective reflexes against mechanical, chemical, and thermal stimuli.[1] In addition to the loss of the protective reflex, reduced corneal sensitivity disrupts the supply of the essential trophic factors (e.g., ciliary neurotrophic factor and nerve growth factor) and neuropeptides (e.g., calcitonin gene-related peptide, substance P, and serotonin) that helps to maintain a healthy corneal epithelium.[2,3] These changes lead to decreased metabolism and mitosis of epithelial cells which may result in persistent epithelial defects (PEDs), stromal thinning, melting, and perforation.[4]

NK is classified as an orphan disease (ORPHA137596) and affects 1-5/10000 people. As the hallmark of the disease is a reduced sensitivity, an underestimation of this number might be in order due to the asymptomatic nature of the initial stages.[4,5]

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All ocular and systemic conditions that impair trigeminal innervation at any level can cause NK. Herpes simplex virus and herpes zoster virus are the most common causes; other causes include chemical burns, chronic use of topical medication, diabetes, neurofibromatosis, or neurosurgical procedures.[6,7] Table 1 gives an overview of the most common ocular, systemic, and iatrogenic causes of NK.

The diagnosis is made by measuring a reduced or absent corneal sensitivity in association with a corneal defect, with or without a previous history of trigeminal nerve damage.[5]

The clinical presentation of NK is classified according to the three-stage classification of Mackie and is based on the extent of corneal involvement. Stage 1 is the most common and is defined by epithelial alterations such as punctate keratopathy, hyperplasia, or irregularity without epithelial defects. Stage 2 is characterized by PEDs without stromal involvement. The defects are commonly found in the superior half of the cornea and have rolled edges. Descemet's membrane folds may be observed. Stage 3 is characterized by epithelial defects with stromal involvement and can progress to a corneal perforation.[8]

Treating patients with NK can be challenging, as presentation is often late due to the asymptomatic nature of the disease. The disease is likely to progress, and the rate of recurrence after healing is rather high due to the lack of innervation. To prevent progression and to avoid secondary complications, treatment should be severity based, started promptly, and closely monitored.[5] Conventional treatment options are aggressive lubrification therapy (artificial tears/tear ointment), punctum plugs, eyelid taping, therapeutic contact lenses (CLs), autologous/allogenic serum, use of botulinum toxin, amniotic membrane grafts, tarsorrhaphy, and/or recombinant human nerve growth factor [Table 2].[9]

Insulin is an anabolic peptide hormone, closely related to insulin-like growth factor, with several physiological functions.[10] It stimulates the haptotactic migration of human epidermal keratinocytes and has been found to promote the healing of ulcerations and burns.[11,12]

The ophthalmic world has taken interest in topical insulin as a therapy for NK due to its low cost and availability. Insulin is present in the human tear film, and insulin receptors have been detected in the human ocular surface and cornea.[13,14] In 1945, Aynsley first reported improvement of corneal ulcers after topical or systemic insulin administration.[15] Recently, insulin has been found to promote *in vitro* corneal epithelial migration which leads to faster wound healing.[16] In addition, topical insulin has been found to delay the degeneration of subbasal plexus corneal nerves in a diabetic mice model, making it a promising treatment option for PEDs and neurotrophic keratitis.[17]

This report systematically reviewed the literature on the efficacy of topical insulin drops in the treatment of epithelial defects with a neurotropic origin. We focused on corneal healing time and recurrence rate as outcome measures.

Table 1: Causes of neurotrophic keratopathy, modified from Semeraro *et al*.[1]

Etiology	
Infections	Herpes simplex
	Herpes zoster
	Mycobacterium leprae
Medication	Anesthetics
	Toxicity of betaxolol, timolol, diclofenac sodium, and sulfacetamide
Ocular surface disease	Chronic blepharitis
	Chemical burns
	Contact lens wear
	Entropion
	Lattice and granular dystrophy
	Ocular trauma
Iatrogenic	Corneal surgery
	Vitrectomy
	Refractive surgery
	The cumulative effect of multiple ocular surgeries
Cranial nerve V palsy	Trigeminal neuralgia surgery
	Neuroplasm
	Aneurysm
	Facial trauma
	Congenital: Riley-Day syndrome, Möbius corneal hypoesthesia
Systemic diseases	Diabetes
	Vitamin A deficiency
	Multiple sclerosis
Miscellaneous	Increasing age
	Adie's syndrome

Table 2: Clinical management of neurotrophic keratitis according to Mackie classification

Stage 1	Stage 2	Stage 3
Artificial tears/ointment	Artificial tears/ointment	Artificial tears/ointment
Eyelid taping	Eyelid taping	Eyelid taping
Punctual plug	Punctual plug	Punctual plug
	Therapeutic contact lens	Therapeutic contact lens
	Autologous/allogenic serum	Autologous/allogenic serum
	Botulin toxin injection	Botulin toxin injection
		Amniotic membrane transplantation
		Conjunctival flap
		Recombinant human nerve growth factor
		Neurotization

Methods

This systematic review was performed and reported in accordance with the Preferred Reporting Items for

Systematic Reviews and Meta-analyses (PRISMA) guidelines.[18]

Inclusion criteria

Selected designs

We selected studies based on their design, quality, and language. Included designs in this literature review were (randomized) controlled trials, open-label studies, cohort studies, case–control studies, case series, case reports as well as studies on animal models. Systematic reviews, abstracts, and expert opinions were excluded. Publications written in a language other than English, Dutch, or Spanish were excluded as were articles published before 2005.

Selected patients

All patients from the selected studies were patients with a neurotrophic epithelial defect. We considered epithelial defects in diabetic patients as part of NK, recognizing that these defects heal with difficulty due to an underlying general neuropathy.[19] There were no inclusion criteria for age, gender, or nationality.

Selected animal models

There was no restriction in the usage of animal models.

Selected interventions

We selected topical insulin eye drops as the intervention for this review and selected studies which reported rate or time until healing of the neurotrophic ulcer as their primary or secondary outcome. Studies that did not have information on the rate or time until the healing of the ulcer were excluded.

Objectives

Primary objective

Systematically review the literature to understand the utility of insulin eye drops as a treatment for neurotrophic keratitis.

Secondary objective

To study in the existing literature whether the effect of topical insulin drops is dose dependent.

Search strategy to identify studies

Databases

We searched the following databases: Medline (through PubMed), Embase, and Web of Science. The results were collected until January 2024.

Search strategies

The same search strategy was used for each database, after adapting it to the style of the different databases [Annexure 1].

Data collection and analysis

Selection of studies

One author selected the studies included in this literature review. The selection process was visualized using the well-known PRISMA flow chart [Annexure 2]. In addition to the electronic search in the abovementioned databases, reference lists of the selected articles were scanned in search of additional relevant papers. This backward scanning did not yield additional research papers.

Data extraction and reporting

All selected publications were evaluated on the presence of the predefined primary and secondary objectives. We presented all the relevant collected data in an outline and formulated a conclusion regarding the usefulness of topical insulin drops in the treatment of PEDs in NK.

Results

Our search strategy yielded 16 original research papers. Each paper is discussed per category and in chronological order (starting with the earliest publication date).

Rodent models

The effect of topical insulin on corneal wound healing in rats with type 1 diabetes mellitus (DM1) has been studied in a rodent model by Zagon *et al*.[20] Streptozotocin was injected to induce DM1 (DB-group, $n = 38$), whereas the healthy control group was injected with citrate buffer (healthy group, $n = 11$).[21] A similar-sized epithelial defect was made in all rats using the same technique (time: 0 h). Antibiotic drops (trimethoprim sulfate and polymyxin B sulfate) were applied to all the eyes following the debridement. Next, the animals of the DB group and the healthy group were randomly assigned to receive either sterile vehicle (SV) or topical insulin at a dose of 1, 2, or 5 insulin units (IU)/drop [Table 3]. The drops were administrated four times daily for 7 days.

The study revealed that DB SV rats had a significantly slower re-epithelialization rate than the healthy SV rats 16, 24, and 32 h after the corneal abrasion. Forty hours after epithelial debridement, residual corneal epithelial defects of the DB SV rats were 32%–37% larger than the healthy SV rats. DB rats treated with 1, 2, or 5 IU/drop had epithelial defects that were 19%–60% smaller than DB SV rats, with the former corresponding to the wound sizes of the healthy SV rats. They reported no differences in the size of the epithelial defect between the 1-, 2-, or 5-IU groups at 16, 24, or 32 h. At 40 h, the results were not significantly different between each groups despite a 60% smaller wound in DB animals receiving insulin compared to the DB SV rats. Topical insulin was not found to alter or enhance the epithelialization in the healthy group. Corneal sensitivity was measured before abrasion of the cornea with an esthesiometer. The DB group showed a 2.6-fold reduced corneal sensitivity compared to the healthy rats. After abrasion, the DB rats treated with 1 IU/drop had a corneal sensitivity that was significantly better than the pretreatment levels and became comparable to the healthy SV group ($P = 0.009$). The effect of other concentrations (2 or 5 IU/drop) on corneal sensitivity was not tested.

To evaluate the effect of topical insulin on DNA synthesis in the corneal epithelium, bromodeoxyuridine (BrdU) labeling was used. The number of BrdU-labeled cells located in the basal layer of the peripheral cornea, limbus, and conjunctiva of DB SV rats was decreased compared to

Table 3: Overview of the concentration and preparation of topical insulin drops

Study (publication year)	Concentration	Type of insulin	Preparation	Side effect
Zagon *et al*. (2007)	1, 2, and 5 IU/drop of 20 µL 4×/day	Bovine insulin (Sigma-Aldrich)	Diluted in moxifloxacin hydrochloride ophthalmic solution (Vigamox Alcon) Commercial applicator bottle Used up to 2 days	None
Bastion *et al*. (2013)	50 IU/mL (1 IU/drop of 20 µL) 4×/day	Actrapid HM 1000 U, Novo Nordisk	Diluted in normal saline Commercial applicator Used up to 3 days after preparation Refrigerated	None
Fai *et al*. (2017)	25 IU/mL (0.5 IU/drop), 4×/day 50 IU/mL (1 IU/drop), 4×/day 100 IU/mL (2 IU/drop), 4×/day	Actrapid HM 1000 U (100 IU/mL), Novo Nordisk	Diluting insulin in normal saline Commercial applicator	None
Diaz-Valle *et al*. (2021, 2022)	1 IU/mL, 4×/day	Study of 2021: Regular insulin Study of 2022: Actrapid (100 IU/mL) (Novo Nordisk)	Diluted in a polyethylene glycol and polypropylene glycol base Sterile amber glass eye drop bottles Refrigerated Used up to 1 month after preparation	None
Soares *et al*. (2022)	1 IU/mL, 4×/day	Fast-acting insulin	Diluted in a propylene glycol base Refrigerated (2°C)	None
Balal *et al*. (2023)	1 IU/mL, 4×/day	Regular recombinant human insulin	Prepared by the pharmaceutical production facility at the Royal Liverpool University Hospital Diluted in a polyethylene glycol and polypropylene glycol base Refrigerated Used up to 1 week after preparation	
Darsrilsyah *et al*. (2023)	25 IU/mL (0.5 IU/drop), 4×/day	Actrapid HM 1000 U (100 IU/mL), Novo Nordisk	Diluted in normal saline	None
Wang *et al*. (2007)	1 IU/mL 2–3×/day	Regular insulin	Diluted in artificial tears with a polyethylene glycol and propylene glycol base Used up to 1 month after preparation Refrigerated	Crystalline keratopathy
Galvis *et al*. (2019)	1 IU/mL 4×/day	Humulin®	Diluted in artificial tears with polyethylene glycol 400/propylene glycol (Systane ultra®)	Leukoma
Bourke *et al*. (2019)	1 IU/mL 3×/day	Actrapid	Diluted in Systane	/
Serrano-Giménez *et al*. (2020)	50 IU/mL (1 IU/drop of 20 µL) 4×/day, 1–2 drops	Actrapid HM® 1000 U, Novo Nordisk	Preparation based on Bastion *et al*. Diluted in normal saline Commercial applicator Used up to 3 days after preparation Refrigerated	None
Tong *et al*. (2020)	25 IU/mL, 6×/day	/	Compounded by a local pharmacy using a sterile technique. No further information	/
Moreker *et al*. (2023)	1 IU/mL, 4×/day	Insulin aspart 100 IU/mL	Diluted in PEG 400-Propylene Glycol eye drops	None
Khilji *et al*. (2023)	1 IU/mL, 6×/day	Regular insulin	Diluted in artificial tears with polyvinyl glycol	None
Giannacarre *et al*. (2024)	1 IU/mL, 4×/day	Humalog® sc 5cart	Prepared by a compounding pharmacy	None

/: Not mentioned

healthy SV rats. Treatment with topical insulin restored the decreased DNA synthesis in diabetic rats to the level of the healthy SV group and differed significantly from the DB SV group ($P < 0.001$). Insulin treatment had no significant effect on the ocular morphological (not further specified) or pathological (e.g., cataract) features, corneal thickness, or intraocular pressure. No effect on serum glucose levels was noted.[20]

Human studies

Clinical trials

The group of Bastion and Ling, located in Malaysia, published a retrospective study. They tested whether topical insulin drops improved the healing of corneal epithelial erosions induced during vitrectomy. Fifteen eyes from fourteen patients who underwent vitrectomy and had an intraoperative debridement ($t = 0$ h), to improve surgical visibility, were

Table 4: Overview of interventional trials

Study	Population	Intervention	Control	Etiology NK	Previous treatment	Epithelial defect (mm^2)	Time until complete healing (mean)	Follow-up period	Toxicity	Conclusion
Bastion *et al.* (2013)	15 debrided eyes 5 eyes D + I 5 eyes D + C 5 eyes ND + C	TI 1 IU/ drop + CT (dexamethasone 0.1% and ciprofloxacin 2 hourly)	CT	Surgery (vitrectomy)	None	D + I: 63.92±12.63 D + C: 63.14±12.40 ND + C: 65.47±11.39	D + I: 60±15 h D + C: 78±30 h ND + C: 65±31 h	120 h	None	TI normalizes the healing rate of epithelial defects in diabetic patients
Fai *et al.* (2017)	33 D-eyes D + I (0.5/1/2 IU) D + C	TI 0.5/1/2 IU/ drop	Normal saline	Surgery (vitrectomy)	None	D + C: 60.32±12.92 D + I (0.5): 62.52±57.16 D + I (1): 57.16±26.43 D + I (2): 59.50±10.04	D + I (0.5): 72 h D + I (1): 144 h D + I (2): 144 h	1 month	None	0.5 IU/drop is the only concentration which is statistically superior to the control group in mean rate of epithelial wound healing
Diaz-Valle *et al.* (2021)	21 eyes with PEDS of which 4 patients with PED due to NK	TI 1 IU/mL	None	Infectious keratitis, calcium keratopathy, previous ocular surgery, lagophthalmos, bullous keratopathy, herpetic eye disease	Vancomycin, ceftazidime, erythromycin, ganciclovir, fluorometholone, AT, CL, AMT, cyclosporine, CS, AS, moxifloxacin, platelet-rich plasma, netilmicin, voriconazole	17.6 (mean)	34.8±29.9 days	3 months after including the last patient	None	2 of the patients with lagophthalmos obtained a complete re-epithelialization Patients who did not obtain re-epithelialization (1 lagophthalmos, 1 herpetic eye disease) showed a reduction in the PED area
Diaz-Valle *et al.* (2022)	61 eyes with PEDs Neurotropic group: 30 patients, 21 case group, 9 control group	TI 1 IU/mL	AS	Infectious, PEDs, neurotrophic PEDs, PEDs due to chronic alterations of the ocular surface, immunomediated PEDs	Lubrication, occlusion, antibiotics, antivirals, doxycycline, CS, AS, cyclosporine, AMT	Case: 14.8±16.2 Control: 18.6±15.0	Case: 32.6±28.3 days Control 82.6±82.4 days	/	None	Significant better healing with TI compared to autologous serum Significant lower need for AMT compared to autologous serum
Soares *et al.* (2022)	21 eyes of which 11 with NK stage 2 and 10 with NK stage 3	TI 1 IU/ mL + CL + Fluoroquinolone drops	None	Herpes simplex keratitis, postpenetrating keratoplasty, diabetes mellitus, central nervous system injury, trauma, topical NSAID abuse	AT, topical and oral antibiotics, CS, antiviral drugs, punctum plugs, CL, AMT, LT	/	NK stage 2: 18±9 days NK stage 3: 29±11 days	Mean 20 months (range, 13–25 months)	/	Significant improvement in BCVA after using TI Mean time of closure is significantly lower in NK stage 2 compared to stage 3

Contd...

Table 4: Contd...

Study	Population	Intervention	Control	Etiology NK	Previous treatment	Epithelial defect (mm²)	Time until complete healing (mean)	Follow-up period	Toxicity	Conclusion
Balal *et al*. (2023)	11 eyes of 10 patients. 2 subgroups; PED with chemical etiology (n=5), PED with nonchemical etiology (n=6)	TI 1 IU/mL	None	Chemical injury, Stevens–Johnson syndrome, mucous membrane pemphigoid, astigmatic keratotomy	AT, CS, CL, chloramphenicol, doxycycline, cyclosporine, AS, AMT, LT, amphotericin, mycophenolate	Chemical: 41±58.5 Nonchemical: 36.6±53.7	Chemical: 39.8±22.5 days, 1 PED did not heal Nonchemical: 67.5±29.7 days, 1 PED did not heal	Mean: 195.7±114.3 days	None	TI led to a resolution in 9 of the 11 PEDs
Dasrilsyah *et al*. (2023)	38 diabetic eyes 19 eyes I 19 eyes C	TI 0.5 IU/mL	AT: Sodium hyaluronate 0.18%	Surgery (vitrectomy)	/	None	I-group: 72 h C-group: 144 h	3 months	None	TI provides a significantly higher healing rate compared tot AT

D: Diabetic, ND: Nondiabetic, C: Control, I: Intervention, TI: Topical insulin, CT: Conventional postoperative treatment, PEDs: Persistent epithelial defects, CL: Contact lens, LT: Lateral tarsorrhaphy, AMT: Amniotic membrane treatment, CS: Corticosteroids, AT: Artificial tears, AS: Autologous serum,/: Not reported, NSAID: Nonsteroidal anti-inflammatory drugs, BCVA: Best-corrected visual acuity, NK: Neurotrophic keratitis

included in the study and divided into three groups; the first group (DTI) consisted of five eyes of diabetic patients who received topical insulin on top of the conventional postoperative treatment to heal the epithelial defect. The topical insulin drops had been instilled four times daily (50 IU/ml, 1 IU/drop) and were discontinued after the corneal epithelial defect was closed. The postoperative conventional treatment consisted of dexamethasone 0.1% and ciprofloxacin 0.3% two hourly in the 1st week. The control arm on conventional treatment consisted of five eyes of diabetic patients (DCT) and five eyes of nondiabetics (NDCT). The epithelial defect had been serially photographed at the time and was measured using local software. The DTI group had a significantly smaller defect size at $t = 24$ h ($P = 0.009$), $t = 36$ h ($P = 0.009$), $t = 48$ h ($P = 0.015$), and $t = 60$ h ($P = 0.005$) compared to the DCT group and had no statistical difference from the NDCT group. The mean time for complete closure was 60 ± 15 h in the DTI group, 78 ± 30 h in the DCT group, and 65 ± 31 in the NDCT group. No systemic or local side effects were reported.[22] Table 4 summarizes the included interventional studies.

Fai *et al*. conducted a Malaysian-based, randomized, double-blind, controlled trial to determine the effect of topical insulin of three concentrations on postoperative corneal wound healing. Thirty-three eyes of 33 diabetic patients, aged from 40 to 75 years, were included. All included patients underwent intraoperative corneal debridement to improve the surgeons' visibility and received topical steroids (dexamethasone 0.1%) and antibiotics (ciprofloxacin 0.3%) two hourly in the operated eye. This medical regime was tapered after 1 week. The patients were randomized into four groups to receive either three different concentrations of topical insulin (DTI 0.5/1/2; topical insulin 0.5/1/2 IU/drop four times a day) or placebo (DNS; topical 0.9% normal saline four times a day). The mean age difference and mean hemoglobin A1c among all groups were not statistically significant ($P = 0.286$ and $P = 0.882$). Subsequently, the rate of corneal epithelial wound healing (mm² per hour) was serially measured from baseline to complete healing. There was no significant difference in the size of the epithelial defect at baseline. After the operation, 96.6% of the epithelial defects healed within 144 h. Only one patient from the DNS group healed on day 8 postoperatively. The peak rate of epithelial healing for all the patients was between 24 and 48 h. The DTI 0.5 group achieved a 100% healing rate within 72 h of treatment, whereas 75% in the DTI 1 group and 62.5% in the DTI 2 and DNS group. The DTI 0.5 group was the only one who was statistically superior ($P = 0.036$) to the control group in terms of the mean rate of epithelial wound healing from baseline to complete healing. The DTI 1 ($P = 0.294$) and DTI 2 ($P = 0.843$) groups did not show any statistical difference compared with DNS.[23]

To evaluate insulin eye drops on PEDs, Diaz-Valle *et al*. published a prospective, nonrandomized, hospital-based study.[24] PEDs were defined as corneal defects with a minimum area of 2 mm² that continue without improvement for more than 2 weeks despite conventional treatment.[25] The study

population comprised 21 adults with PEDs in one or both eyes. The etiology varied from infectious keratitis (33%), calcium keratopathy (24%), ocular surgery (14%), lagophthalmos (14%), bullous keratopathy (10%), and herpetic eye disease (5%). All included patients received topical insulin eye drops at a concentration of 1 IU/ml every 6 h. The use of topical insulin was evaluated 3 months after including the last patient. At the time of evaluation, 17 patients (81%) had a complete closure of the PED and four patients (19%) still had an epithelial defect. In patients with an epithelized cornea, the mean time until complete closure was 34.8 ± 29.9 days (median 23; range, 7–114). Patients who still presented with an epithelial defect had a mean PED area reduction of 91.5%.

As mentioned above, patients with lagophthalmos and herpetic eye disease were also included in this cohort. Of the three patients with lagophthalmos, two patients obtained complete re-epithelialization. The patient with an incomplete re-epithelialization had a reduction of 94% in the PED area 61 days after starting topical insulin treatment. The only patient who presented with a herpetic eye disease did not have a complete re-epithelialization of the cornea. However, there was a reduction of 91% in the PED area 65 days after initiating topical insulin drops. No adverse effects or recurrences of the epithelial defects were reported.[24]

Following the earlier study, the same research group published a controlled study, comprising the cases published in 2021. The main goal of this study was to evaluate the effect of topical insulin on PED epithelialization compared to autologous serum. The second efficacy point was to evaluate the need for amniotic membrane transplantation (AMT) or other surgeries. The study included 61 patients treated with insulin eye drops 1 IU/ml (case group) and 23 patients treated with autologous serum (control group). Both groups received the topical treatment four times daily. When the PED healed within 2 weeks, it was labeled as a success, whereas healing within 1 month was labeled as a partial success. No differences in patient demographics, previous ophthalmic conditions, treatment, or surgery were noted. The patients were divided according to PED etiology into the following groups: infectious, neurotropic, chronic alterations of the ocular surface, and immunomediated. Epithelialization was achieved in 84% of the insulin group and in 48% of the patients treated with autologous serum (P = 0.002). In patients where PED closure was achieved, the mean time until re-epithelialization was 32.6 ± 28.3 days (range, 4–124) in the insulin group and 82.6 ± 82.4 (range, 13–231) in the autologous serum group (P = 0.011). No differences were found in the epithelialization rate between diabetics and nondiabetics. The recurrence rate was significantly higher in the autologous serum group (43% vs. 11%, P = 0.002). The need for AMT was significantly lower in the insulin group (P = 0.005). The neurotrophic group consisted of 30 people; of whom, 21 were treated with topical insulin and nine with autologous serum. It included the following etiologies: herpetic keratitis, damage of the trigeminal nerve, lagophthalmos, postinfectious, and ophthalmologic surgery. Mean pretreatment areas were significantly higher in the insulin group compared to the autologous group (9.4 ± 20.4 mm² vs. 19.2 ± 12.7 mm², respectively, P = 0.003). Epithelialization was achieved in 20 patients (95%) on insulin and four patients (44%) on autologous serum (P = 0.005). The need for AMT was significantly lower in the insulin group compared to the insulin group (P = 0.020). For results, no distinction was made between the different etiologies of the neurotrophic PEDs. No adverse events were reported.[26]

Soares *et al*. conducted a retrospective, observational, single-center study to evaluate the clinical outcome of patients with stage 2 or 3 NK treated with topical insulin. The study included 20 patients, of which 11 eyes were with NK stage 2 and 10 eyes were with NK stage 3. All patients received topical insulin four times daily at a concentration of 1 IU/ml. A therapeutic CL was placed in every patient. Fluoroquinolone drops were applied to prevent CL-related side effects. Treatment was continued until the PED was completely closed. Within 7–45 days of treatment, 90% of the patients had a complete closure of the PED. The mean time until complete closure was significantly lower in NK stage 2 (18 ± 9 days) compared with stage 3 (29 ± 11 days) (P = 0.023). In both groups, the patients had significant improvement in best-corrected visual acuity (BCVA) after using topical insulin (NK stage 2; P < 0.001 and NK stage 3; P = 0.004). However, the improvement of the BCVA was higher in the NK stage 2 group as well as the final BCVA compared to the NK stage 3 group. During the follow-up period (mean period of 20 months, ranging from 13 to 25 months), two patients had a recurrence of the epithelial defect which achieved complete re-epithelialization when the insulin drops were reinitiated. In the two unsuccessful cases, it was not possible to place a CL. One patient did not achieve complete closure after 42 days of treatment. The other unsuccessful case achieved partial improvement with topical insulin. After performing a lateral temporary tarsorrhaphy, a complete re-epithelialization was achieved after 41 days.[27]

Balal *et al*. published a prospective interventional study. Eleven eyes of ten patients were included. All patients had a refractory PED either from chemical eye injuries (n = 5) or no chemical-related events (Stevens–Johnson syndrome [n = 2], mucous membrane pemphigoid [n = 3], and astigmatic keratotomy [n = 1]).

Eighty-two percent of the included eyes showed a complete re-epithelialization after receiving topical insulin drops four times daily for 2 months on a weekly basis. The mean time until re-epithelialization was 62.3 ± 34.6 days (range, 14–112). Two patients, of whom one with a defect due to chemical trauma, did not achieve complete closure of the epithelial defect. If complete epithelialization was achieved, no recurrence in epithelial defect was observed in the follow-up of 195.7 ± 114.3 days. We consider PEDs from chemical burns part of NK. Eighty percent of the eyes with PEDs from

chemical injuries achieved a complete re-epithelialization within a mean time of 39.8 ± 22.5 days; one person did not respond to topical insulin drops. This is in comparison to a mean healing time of 67.5 ± 29.7 days in PEDs due to nonchemical events. No adverse effects were reported.[28]

Dasrilsyah *et al*. determined and compared the effect of topical insulin versus artificial tears on the healing rate of postoperative corneal epithelial defects in a prospective, randomized controlled study. Thirty-eight eyes from 38 diabetic patients were included; all patients had an epithelial defect which was induced during surgery ($t = 0$). They received a similar postoperative treatment of topical steroids (dexamethasone 0.1%), antibiotics (ciprofloxacin 0.3%), and a topical gel that consisted of a steroid–antibiotic combination (neomycin sulfate, polymyxin B sulfate, and dexamethasone 0.1%). Patients were randomized into two groups to receive either topical insulin (DTI; topical insulin 0.5 IU/drop) or artificial tears (DTA; sodium hyaluronate) four times a day. The two groups did not differ in demographic variables. Seventy-two hours after the cornea debridement, all epithelial defects of the DTI group were closed; this is in contrast to the DTA group where the defects were closed after 144 h. When evaluating the healing rate from baseline to closure, the group concluded that the DTI group had a significantly higher healing rate compared to the DAT group at different time points. Up to 48 h, this was significantly different. The peak rate of corneal epithelial wound healing was between 12 and 36 h for both groups. No adverse effects were reported.[29]

Case reports

Wang *et al*. presented a case series of six patients, aged 2–73 years. All patients had sterile neurotrophic corneal ulcers that were 2–5 months refractory to previous medical and surgical treatments (lubrification, antibiotic ointment, therapeutic CLs, amniotic membrane graft, tarsorrhaphy, and inferior rectus recession to encourage Bell's phenomenon). Treatment with topical insulin, two to three times daily (1 IU/ml), resulted in a complete healing within 7–25 days (average, 13.5 days). One case developed crystalline keratopathy 4 months after the initial presentation. The research group attributed this keratopathy to chronic topical steroid use.[30]

Galvis *et al*. published a case of a 48-year-old female who underwent a resection of an acoustic neurinoma. She presented with a combination of an exposure keratopathy and neurotropic keratopathy due to a facial nerve palsy and an impaired innervation by the trigeminal nerve. The epithelial defect was treated with lubrification therapy. The lesion evolved 2 weeks later to an infectious keratitis. Topical antibiotics were added, and the infection was resolved. However, the epithelial defect did not respond to the medical treatment for 1 month. Topical insulin four times daily was indicated (1 IU/ml). It showed a decrease in lesion area in the following 5 days. A CL was associated to heal the remaining epithelial defect. The epithelial defect completely closed 14 days after starting the topical insulin treatment. She developed a paracentral leukoma 4 months later.[31]

Bourke described a case report of an 8-year-old girl with a background history of neurofibromatosis type 2, a meningioma of the left optic nerve, and a denervation of the left cornea. She developed a stage 2 neurotrophic ulcer in her left eye, and topical treatment with dexamethasone drops and eye lubricants was started. On returning from vacation, she was hospitalized with a hypopyon and lower corneal infiltrate (5 mm × 2 mm). After receiving oral ciprofloxacin and topical vancomycin and ceftazidime drops, the hypopyon reduced in size. A lateral tarsorrhaphy was performed. At discharge, her medication list consisted of topical prednisolone, VitA-POS®, HYLO-forte®, and chloramphenicol ointment. As the ulcer was not healing 1 week after infectious control, topical insulin drops (1 IU/ml) were commenced three times daily, and a decrement of the corneal epithelial defect was described. The study did not indicate whether complete epithelialization was achieved.[32]

In 2020, a case report was published of a 41-year-old male who accidently spilled the contents of a car battery in both his eyes. This accident resulted in an epithelial defect in the lower right eye and in the whole left eye. The right eye completely healed within 1 week after a therapeutic CL was placed, and tobramycin, dexamethasone, and atropine eye drops were prescribed for 1 week. The left eye showed a persistent corneal ulcer which was refractory to both pharmacological and surgical treatment for 4 years and finally resulted in a corneal perforation. Treatment with corticoids, antibiotics, autologous serum, artificial tears, therapeutic CLs, penetrating keratoplasty, amniotic membrane coating, and corneal trephination did not have the intended effect. Treatment with topical insulin 50 IU/ml (1 IU/drop), one–two drops four times daily, was started. The epithelial ulcer showed a regression in size 2 months later. At the time of publishing, the patient has been treated for 3 months and showed a complete healing of the epithelial defect. No side effects were reported. There is no further information regarding the follow-up.[33]

Tong *et al*. presented a case of a 55-year-old patient with severe hypoesthesia and poorly controlled diabetes mellitus. The patient had a bilateral neurotrophic ulcer which was resistant at the following treatments: preservative-free artificial tears, moxifloxacin drops, oral valacyclovir, topical prednisolone, therapeutic CLs, and a temporary tarsorrhaphy. All other therapies were stopped before the patient received the insulin drops six times per day in each eye (25 IU/ml). There was almost a complete re-epithelialization in both eyes 1 week later. The study provided neither any information about the complete closure of the ulcers nor the follow-up period.[34]

Moreker *et al*. presented two cases where topical insulin was used to manage NK unresponsive to conventional treatments. A 55-year-old male, with a history of neurosurgery followed by right facial palsy which required permanent tarsorrhaphy,

presented with a central corneal ulcer on the right eye. Twenty-five days after associating topical insulin drops (1 IU/ml) to the lubricants, the ulcer was healed.[35]

In another case, a 41-year-old diabetic male developed NK despite temporary tarsorrhaphy and intense lubrication. Permanent tarsorrhaphy and AMT resulted in partial resolution of the NK. Complete resolution was achieved after the introduction of insulin eye drops. The treatment duration for initiation of topical insulin drops was not provided in either case.[35]

Khilji *et al*. used topical insulin as an early treatment option for NK in a 64-year-old male with NK secondary to prior herpetic keratitis. He presented with bilateral corneal opacities and a corneal ulcer (4 mm × 6 mm) in his left eye. Treatment was initiated with oral acyclovir 400 mg twice a day, topical acyclovir ointment 5% five times a day, and topical insulin drops (1 IU/ml) six times a day. After a month, the corneal ulcer reduced, and after 2 months, it was fully re-epithelialized.[36] The patient was under acyclovir ointment until the healing of the ulcer despite its well-known toxic effect on epithelial healing.

In 2023, Giannaccare *et al*. documented the case of a 40-year-old male with NK following surgical and adjuvant radiotherapy for adenoid cystic carcinoma of the nasal cavity with basicranial involvement. The patient presented with a persistent central epithelial defect that did not respond for months to conventional treatments. Topical insulin drops (1 IU/ml) were started, and a therapeutic Hyper-CL soft CL was applied to increase the contact time between the drops and the corneal surface. After 20 days, the epithelial defect was fully healed.[37]

Discussion

The primary objective of this literature review was to investigate whether topical insulin drops are useful in the treatment of epithelial defects in NK. We collected 16 research articles for this purpose, including 1 animal model study, 2 randomized controlled trials, 2 controlled trials, 3 open-label trials, and 8 case reports/series. This review article also included PEDs in patients with DM, given a reduced corneal sensitivity in these patients is due to the general neuropathy.[19]

Through research into alternative treatment options to influence blood sugar levels, Christie and Hanzal first mentioned the topical ocular route of insulin in 1931. They reported that topical insulin did not affect serum glucose levels.[38] Subsequently, Aynsley reported the use of insulin as a treatment for corneal ulcers, as he described five heterogeneous cases who showed improvement of the epithelial defect after receiving insulin. It was not specified whether they were diabetic.[15] In the next five decades, the use of topical insulin drops ended up in the oblivion until Zagon *et al*. reinstated the potential advantage of this therapeutic regimen in 2007. The effect of topical insulin on corneal wound healing was studied in diabetic rodent models. They showed for the first time that topical insulin can normalize the reduced corneal re-epithelialization in diabetic rats. No difference was reported when treating with either 1, 2, or 5 IU/drop. The results in this study were significant at 16, 24, and 32 h. Forty hours after the corneal debridement, the results were not significant despite a 60% smaller wound size in diabetic animals treated with topical insulin compared to diabetic rats who received SV.[20] This can be attributed to the fact that most epithelial defects, in both groups, had already healed. The group also concluded that topical insulin therapy is only useful in diabetic rats, as it was not found to alter corneal epithelialization in nondiabetic rats.[20] This can be explained by the fact that the nondiabetic rats already showed normal corneal sensitivity before the administration of topical insulin. It is possible that topical insulin drops do influence nondiabetic rats in which corneal sensitivity is reduced.

Bastion and Ling extrapolated the results of the animal studies of Zagon *et al*. to diabetic patients who underwent a vitrectomy. They confirmed that topical insulin drops can normalize the healing rate of epithelial defects.[22] Similar results were published by Fai *et al*. Their study allowed a direct comparison of topical insulin in three concentrations for the treatment of epithelial defects. Insulin drops at a concentration of 0.5 IU/drop achieved a 100% corneal epithelial healing which was significantly superior to all other concentrations and placebo.[23] The same concentration was used to heal a bilateral neurotrophic ulcer in a poorly controlled diabetic.[34] This concentration differed from the above-mentioned study by Bastion and Ling where 1 IU/drop was used.[22]

Experience with topical insulin for corneal wound healing in nondiabetic patients is limited. All patients included in the case series of Wang *et al*. (n = 5) achieved complete re-epithelialization within 7–25 days when treated with topical insulin at a concentration of 1 IU/ml.[30] This was the first case series that suggested that topical insulin may benefit both nondiabetic and diabetic patients. This is contrary to the conclusion of Zagon *et al*. who stated that topical insulin cannot alter the epithelialization in nondiabetic animals.[20] The finding that topical insulin may benefit nondiabetic patients has been confirmed over the years by several research groups, all using the same concentration of 1 IU/ml.[24,26,31,32] In the case report of Serrano-Giménez *et al*., epithelialization was achieved with a higher concentration of topical insulin (50 IU/ml).[33]

Soares *et al*. were the first to stratify their patients for their NK stage. This study used therapeutic CL as an adjuvant treatment to the topical insulin drops. Ninety percent achieved complete epithelialization within 7–45 days. Interestingly, the therapeutic CL could not be placed on the patients who did not achieve completed epithelialization.[27] This suggests that CL can be an adjuvant treatment option with topical insulin drops, either by protecting the brittle surface or by prolonging the longer contact time of the insulin drops. The mean number of days until complete closure of the PED was lower, and the improvement in BCVA was higher in the NK stage 2 group compared to the NK stage 3 group.[27] This finding is expected given the fact that stage 3 patients have more pronounced corneal damage.

When looking at the healing times, we notice that both Diaz-Valle *et al*. and Soares *et al*. have a longer healing time compared to Wang *et al*. despite using the same concentrations of topical insulin drops. This may be explained by the fact that the epithelial defects, at the start of topical insulin treatment, were larger in the study of Diaz-Valle *et al*. compared to Wang *et al*. or that they were classified in other stages of NK [Table 5]. In the study of Soares *et al*. and Diaz-Valle *et al*., it can also be attributed to the more diverse etiologies of the epithelial defects.[26,27,30]

Two of the included studies compared the use of topical insulin with current therapy for NK. Diaz-Valle *et al*. compared topical insulin with the use of autologous serum in refractory PEDs. They divided patients according to the cause of the PED. The study proved that people with neurotropic PEDs had significant better epithelial healing when treated with topical insulin and that the need for AMT was significantly lower compared to the autologous serum group.[26] The research group of Dasrilsyah *et al*. was able to demonstrate that topical insulin drops (0.5 IU/drop) have a higher healing rate from baseline to closure compared to artificial tears in diabetic patients. This difference is only significant up to 48 h after corneal debridement which can be explained by the fact that the epithelial defects in the insulin group were already closed and the defects in the artificial tears group were already reduced.[29]

Throughout our literature review, we noticed the diversity in used concentration and solvents used. Table 3 summarizes the concentration and preparation process of the topical insulin drops per research group. Most of the included studies used fast-acting insulin diluted in normal saline 0.9% or artificial tears based on a polyethylene glycol and propylene glycol base. The drops were kept refrigerated. Zagon *et al*. used their drops up to 2 days, whereas Wang *et al*. and Diaz-Valle *et al*. used their drops up to 1 month.[20,24,30]

Looking at the type of insulin, we find that different types were used namely ultra-fast acting insulin analogues, fast-acting analogues and intermediate acting analogues. Most of the studies used a fast-acting insulin: Actrapid[22,23,27] showed a shorter healing time compared to patients treated with a regular insulin.[24,30] All the types of insulin have different pharmacokinetic properties. If topical insulin has a limited stability on the corneal surface, it may be more favorable to use a fast-acting insulin.

Another finding is that the studies with faster healing time mostly used a polyethylene glycol and propylene glycol vehicle. Since these drops are also used to stabilize the tear surface, this may be additive to the effect of topical insulin drops. The possible presence of preservatives in these vehicles may also affect the healing process.

The used concentrations varied between 1 and 100 IU/ml. This is remarkable as these concentrations differ by a factor of hundred. Zagon *et al*. was the first research group to state that 1 IU/drop (50 IU/ml, 1 drop constitutes 20 µl) four times daily had a significant faster epithelial healing rate in diabetic rats compared to the control.[20] The study does not specify the data they rely on. Fai *et al*. on the other hand showed that 25 IU/ml or 0.5 IU/drop four times daily was the only concentration that was statistically superior to the control group in the mean rate of epithelial wound healing.[23] In nondiabetic cases, concentrations of 1 IU/ml up to 50 IU/ml were used at various frequencies. The finding that a lower concentration is better for epithelial wound healing can perhaps be explained by a difference in osmolarity in the preparations. One would expect drops with lower osmolarity to have a more beneficial effect on the treatment of NK. Hyperosmolar drops can cause irritation and inflammation which do not enhance corneal healing.

Further investigation is needed to evaluate the correct dosage and frequency for both diabetic and nondiabetic patients. Corresponding authors of all reviewed papers were contacted, to understand their rationale of the chosen concentrations. Unfortunately, nonresponded to our additional questions, leaving this important question to date unanswered.

All included studies, except for two, reported the absence of local or systemic side. This was regardless of the concentration of insulin drops used. Insulin does not affect corneal thickness, ocular pressure, or serum glucose levels.[20] Bartlett *et al*. proved that long-term use (8 weeks) of topical insulin in an isotonic sodium chloride solution is not harmful to human corneal and conjunctival tissues at concentrations up to 100 IU/ml.[39] The crystalline keratopathy mentioned in the study by Wang *et al*. is probably secondary to the chronic use of topical insulin drops.[30] This correlation has been described in the past.[40] Galvis *et al*. described 4 months after cessation of insulin drops the presence of a leukoma where previously the infiltrate was localized.[31]

The mechanism by which topical insulin could improve ulcers in diabetic and nondiabetic patients is not fully understood. Several mechanisms have been proposed. Shanley *et al*. demonstrated that topical insulin facilitated epithelial closure of small corneal wounds *in vitro* by enhancing epithelial cell migration through phosphorylation of ERK 1/2 and Akt.[16] Fai *et al*. confirmed this suggestion, as most patients achieved their peak rate of epithelial healing between 24 and 48 h, which correlates with the migration phase during the process of corneal epithelial healing known to occur around 24–48 h after corneal epithelial injury.[23] This can be confirmed by Dasrilsyah *et al*. as their study shows a peak rate of epithelial healing between 12 and 36 h.[29]

While Shanley *et al*. could not demonstrate that proliferation plays a role in corneal epithelial healing,[16] Zagon *et al*. suggested that epithelial proliferation may be a mechanism for enhancing epithelial healing, as topical insulin restored the decreased levels of DNA synthesis of basal epithelial cells to normal value.[20] Another proposed mechanism is the restoration of corneal nerves, as topical insulin has been shown to slow the loss of subbasal plexus corneal nerves.[17]

Our review paper is limited due to the small sample sizes of the included papers. Inclusion is hampered due to the

Table 5: Overview of all the case reports

Study	Number of treated patients	Age (years)	Sex	DM	Etiology NK	Size epithelial defect (mm^2)	Previous treatment	Treatment scheme	Complete healing time (days)	Follow-up	Recurrence	Side effect
Wang *et al.* (2007)	1	2	Female	/	Lagophthalmos with absent corneal sensation after an excised teratoma	28	LT, inferior rectus recession	3×/day Tapered to 1×/day after healing	14	18 months	No	No
Wang *et al.* (2007)	2	2	Male	/	Hyposensitive cornea	32.5	Antibiotic ointment, AMT	3×/day Tapered to 2×/day after healing	13	1 year	No	No
Wang *et al.* (2007)	3	23	Female	/	Herpes zoster	6	CL	2×/day Stopped after healing	25	/	/	No
Wang *et al.* (2007)	4	74	Female	DM on lispro	Cranial nerve injury	3.8	LT	2–3×/day 2 IU lispro in 10 ml artificial tears) Continued for 3 weeks	7	/	/	No
Wang *et al.* (2007)	5	71	Female	/	Nonhealing epithelial defect following vitrectomy	16	Lubrification, CL, LT	2×/day 1×/day after healing Stopped after 1 month	14	1 year	No	No
Wang *et al.* (2007)	6	73	Female	/	Herpes zoster	3.8	LT, AMT, CS	3×/day	8	/	Infectious ulcer 4 months after presentation Healed with insulin drops	Crystalline keratopathy
Galvis *et al.* (2019)	1	48	Female	/	Facial and trigeminal paralysis	39.7	AT, moxifloxacin, dexamethasone, vancomycin, CL	4×/day	14 (insulin + CL)	4 months	No	Leukoma
Bourke *et al.* (2019)	1	8	Female	/	Corneal denervation	10	CS, AT, vancomycin and ceftazidime drops, oral ciprofloxacin, VitA-POS, HYLO-forte, chloramphenicol ointment, LT	3×/day	/	/	/	/
Serrano-Giménez *et al.* (2020)	1	41	Male	No	Postcaustic	/	Debridement, CL, Tobramycin, CS, atropine, diclofenac, AS, AT, penetrating keratoplasty, AMT, corneal trephination	4×/day, 1–2 drops	Between 2 and 3 months	3 months	/	No
Tong *et al.* (2020)	1	55	Male	Yes	Severe hypoesthesia + DM	OD: 33.8 OS: 15	AT, moxifloxacin drops, oral valacyclovir, CS, CL, LT	6×/day, 1 drop	/	/	/	/
Moreker *et al.* (2023)	1	55	Male	/	Right facial palsy after neurosurgery	/	LT, AT	4×/day, 1 drop	25 days	4 months	No	No

Contd...

Table 5: Contd...

Study	Number of treated patients	Age (years)	Sex	DM	Etiology NK	Size epithelial defect (mm²)	Previous treatment	Treatment scheme	Complete healing time (days)	Follow-up	Recurrence	Side effect
Moreker *et al.* (2023)	2	41	Male	Yes	DM	/	LT, AMT	4×/day, 1 drop	8 days	7 months	No	No
Khilji *et al.* (2023)	1	64	Male	/	Herpetic keratitis	4 mm×6 mm	No previous treatment	6×/day, 1 drop	2 months	/	/	No
Giannaccare *et al.* (2024)	1	40	Male	/	Surgical and adjuvant radiotherapy for adenoid cystic carcinoma of the nasal cavity with basicranial involvement	7 mm×4 mm	AT, vitamin A ointment, punctum occlusion, AS, CL, CS	4×/day+Hyper-CL soft CL	20 days	3 months	NO	No

/: No information, DM: Diabetes mellitus, NK: Neurotrophic keratopathy, LT: Lateral tarsorrhaphy, AMT: Amniotic membrane treatment, CL: Contact lens, CS: Corticosteroids, AT: Artificial tears, AS: Autologous serum, OD: Right eye, OS: Left eye

rarity of NK, decreasing the statistical power. Furthermore, Diaz-Valle *et al*., Soares *et al*., and Balal *et al*. lacked a control group to compare effectiveness.[24,27,28] Bastion and Ling and Fai *et al*. had a control group, but it was a historical control group.[22,23] Only two studies compared topical insulin with an established treatment option.[26,29] Looking at the included cases, we noticed a heterogeneous patient profile in terms of etiology, previous treatment, and size of the initial defect. The follow-up period varied from 48 h to 20 months. Studies with a short study period could not provide information about the recurrence rate of the epithelial defects or late-onset complications.

In conclusion, this review article shows that topical insulin is a promising and effective (adjuvant) treatment for NK. There are several advantages in using topical insulin drops; insulin is widely available, and it is relatively inexpensive compared to autologous serum and recombinant human nerve growth factor. They do not affect systemic blood glucose levels and are well-tolerated. Unlike autologous serum, no blood sampling is required to prepare the drops.

However, further stability testing of the insulin eye drops is needed, followed by prospective, randomized controlled trials to evaluate the best posology, concentration, solvent, duration, and side effect of topical insulin treatment for (non) diabetic patients with NK.

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Conflicts of interest
There are no conflicts of interest.

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Annexures

Annexure 1: Search strategy

Medline:

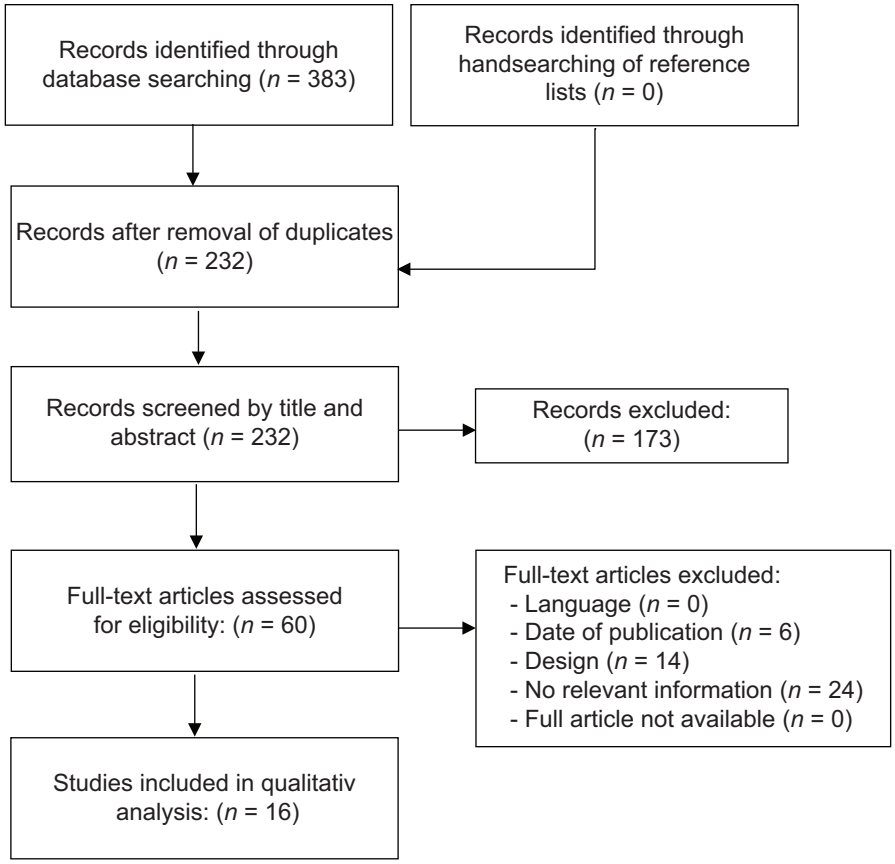
("insulin"[Mesh] OR insulin*[tiab]) AND ("Corneal Ulcer"[Mesh] OR "keratitis"[Mesh] OR corneal-ulcer[tiab] OR "keratitis"[tiab] OR "keratitides"[tiab] OR keratopath*[tiab] OR corneal-epithelial-defect*[tiab] OR neurotrophic cornea [tiab])

Embase:

('insulin'/exp OR 'insulin*':ti, ab, kw) AND ('keratitis'/exp OR 'cornea ulcer'/exp OR 'keratitis':ti, ab, kw OR 'keratitides':ti, ab, kw OR 'cornea inflammation':ti, ab, kw OR 'corneal inflammation':ti, ab, kw OR 'keratopath*':ti, ab, kw OR 'corneal epithelial defect':ti, ab, kw OR 'cornea ulcer':ti, ab, kw OR 'neurotrophic cornea':ti, ab, kw)

Web of Science:

"insulin*" AND "corneal ulcer" OR "keratitis" OR "keratopath*" OR "corneal epithelial defect*" OR "neurotrophic cornea" OR "cornea inflammation" OR "corneal inflammation"



Annexure 2: PRISMA flow diagram