Effects of topical insulin on wound healing: a meta-analysis of animal and clinical studies

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Abstract. Various researches have reported that the application of topical insulin improves wound healing. Considering the lack of a quantitative comprehensive research on this matter, we conducted a meta-analysis of clinical research and experimental animal studies. Prospective and randomized controlled trials of PubMed, Embase, and Cochrane Library were conducted using appropriate search strategies to compare the effectiveness of topical application of saline and insulin on wounds. The standardized mean difference was calculated as follows: wound healing time, wound healing rate, wound area, and the percentage of wound contraction. Each study used the Cochrane risk-of-bias tool and RevMan 5.3 software to create aggregated assessments and forest plots. The quality of evidence was evaluated in accordance with the methods of the Grading of Recommendations, Assessment, Development and Evaluation working group. Four clinical and nine animal studies eligible for inclusion were included in the meta-analysis. The assessments for clinical studies were as follows: wound healing time, –2.48 [–3.44, –1.51] and wound healing rate, 22.23 [18.17, 26.28]. Meanwhile, for animal studies, the following assessments were noted: wound healing time, –1.27 [–1.75, –0.79]; wound contraction rate, 15.91 [13.88, 17.95]; and wound area, –19.3 [–21.16, –17.44]. For the measurement of the following results, only one animal study was performed, pericyte recruitment of microvessels. Based on the analysis, it can be preliminarily judged that application of topical insulin can aid wound healing.

Key words: Wound healing, Topical insulin, Insulin therapy, Meta-analysis

WOUND HEALING has a very complex course. When the skin is wounded, several phases, such as hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodeling, take place in a temporal sequence but also overlap [1]. Nevertheless, the duration of each period varies depending on wound type, management, and microbiologic, immunologic, and physiologic factors [2]. It is estimated that as many as 4.5 million people suffer from chronic wounds in the United States, leading to enormous economic and psychosocial spending [3]. Elderly patients and those with diabetes are particularly prone to abnormal wound healing resulting in long-term sequelae. Disturbance of carbohydrate metabolism, dysregulation of inflammatory response, insufficiency in growth factor secretions, and dysfunction of cell repair and cell signaling are all related to the morbidity of diabetic wound healing [4-6]. It is known that diabetes mellitus is a chronic metabolic disease that causes many complications, such as diabetic neuropathy. The sensory loss in diabetic neuropathy augments at seven times the risk for foot ulceration, and 25% of patients with diabetes are likely to suffer from diabetic foot ulcer, which is the leading cause of nontraumatic lower limb amputations in a patient’s lifetime [7, 8]. Insulin is a kind of polypeptide hormone and growth factor that has several physiological functions, and it is mainly known to regulate blood glucose levels. Insulin has been used for the treatment of chronic wounds since the early 20th century [9, 10]. Researches have confirmed that insulin is effective in irritating angiogenesis and thus expedites wound healing with ameliorative quality of healed tissue [11]. Furthermore, insulin irritates the migration of human epidermal keratinocytes by activating a transcription factor called nuclear factor kappa B (NF-κB) [12]. Some animal and clinical studies have evaluated the role of topical insulin in wound healing; however, the meta-analysis between these two different types of researches is nonexistent. The purpose of this meta-analysis was to assess the effectiveness of topical insulin in wound healing on animal and clinical researches.
Materials and Methods

Search strategy
We explored prospective researches and randomized clinical trials (RCTs) published until September 2019 in the following databases: PubMed, Embase, and Cochrane Library. There was no publication date or language limit. The terms “insulin” AND “wound” were used to search studies.

Inclusion and exclusion criteria
Studies that conformed to the following criteria were included: (a) adults and animals that exhibit acute wounds, such as burn or surgical wounds, and chronic wounds, such as pressure ulcers or diabetic foot ulcers; (b) the experimental group were administered topical insulin; (c) the effects were compared between experimental and control groups, such as wound healing rate, wound healing time, wound area, vessel density, and the percentage of fibrosis and collagen deposition.

Publications from case reports, reviews, letters, and studies without raw data or controls were excluded. If multiple articles were published with the same population and on the basis of one study, we wound chose either the article with the latest published date or the date with the maximum sample size.

Data extraction and quality assessment
Information from each research was extracted independently using a standardized data extraction form by two researchers (Liu and Wang). The general characteristics of each study, the type of wound, and the results were recorded and double-checked where possible and appropriate. The data set were acquired by communicating with the authors. Any disagreements were settled by consensus (Xu). The non-Cochrane mode in RevMan 5.3 software was used to analyze the extracted data. Both authors used the Cochrane collaboration’s tool to evaluate the risk of bias and independently assess the methodological quality of eligible animal and clinical studies. According to the guidelines, we estimated whether experiments took enough procedures to decrease the risk of bias through six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. The quality of information of RCTs was graded as unclear or low or high risk of bias [13].

Statistical analysis
Standardized mean difference (SMD) was used to summarize the analysis of individual studies’ consequences. SMD was selected as a measure of aggregate results due to the variability observed in the continuous outcome scale. Cohen [14] advised that SMD was classified as small, medium, and large based on thresholds of 0.2, 0.5, and 0.8, separately. The deviation from the point estimation for both individual studies and the synthesized estimation were represented by 95% confidence interval (CI). The heterogeneity between the studies was visually evaluated using a forest plot, where >30% of I² statistics was thought to have moderate-to-severe heterogeneity, and a Chi-square test with a statistical p-value of <0.10 indicating statistical significance. Once the moderate-to-severe heterogeneity, otherwise fixed-effect, models were generated, the random-effect models were then used. The meta-analysis in this article was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The quality of evidence was graded according to the approach used by the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) working group. The subgroup analyses were between patients with and without diabetes in clinical studies or between animals with and without diabetes in animal studies.

Ethical approval
Our study was a meta-analysis belonging to secondary analysis so there was no need for an ethical approval.

Results

Search results and details of the included studies
A total of 6,363 articles were obtained through the above search strategy. After evaluating the qualification of the accredited research, a total of 13 studies, including four [16-19] clinical studies and nine [11, 16, 20-26] animal studies, were found suitable to be involved in this review. The study flow chart is presented in Fig. 1. Table 1 contains a list of the primary features of each animal study. Only two studies [11, 24] on animals with diabetes were performed, and five studies [16, 20-22, 25] were performed in animals without diabetes. BAIRY et al. [23] and ÖZAYDIN et al. [26] included animals with and without diabetes in their study, in whom the percentage of wound contraction and wound size were analyzed. Likewise, Table 2 illustrated the main characteristics of individual clinical trial. Three studies [17-19] included patients without diabetes only. Greenway et al. [16] included patients with and without diabetes in their trials and examined the wound healing rate only.

Therefore, for this result analysis, population with and without diabetes were separately included in clinical data, and similarly, the animal data was respectively included for animals with and without diabetes. The risk
of bias of the individual animal researches is described in Fig. 2a, whereas Fig. 2b depicts the risk of bias of the individual clinical studies.

**Pooled results**

**Wound healing time (animal)**

A total of five studies (86 animals) compared the wound healing time between topical insulin and normal saline, and the synthesized result turned out to favor topical insulin (Fig. 3a). However, the subgroup analyses between animals with and without diabetes were not significant (Fig. 3a).

**Percentage of wound contraction (animal)**

Two studies assessed the percentage of wound contraction with topical insulin application in 36 animals, of which data from both animals with and without diabetes were included from one research. Topical insulin significantly enhanced the wound contraction percentage compared with normal saline (Fig. 3b). The subgroup analyses between animals with and without diabetes also showed significant differences (Fig. 3b).

**Wound area (animal)**

A total of 120 animals were evaluated for the wound area treated with topical insulin and compared with the control group in two studies, of which data from both animals with and without diabetes were included from one research. The pooled result was in favor of topical insulin (Fig. 3c), and the subgroup analyses between animals with and without diabetes were also significant (Fig. 3c).

**Other outcome measures (animal)**

There was only one study directing at outcome measures (pericyte recruitment of microvessels) not included in the pooling of results.

**Wound healing time (clinical)**

Two studies involving 67 patients evaluated the healing time of the wound between the group using topical insulin and the control group. Data from both those with and without diabetes were included from one research. Local insulin decreases wound healing time significantly.

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**Fig. 1** Study flow diagram

A total of 4 clinical and 9 animal studies were found eligible to be included in the systematic review for quantitative synthesis.
### Table 1  Summary of key characteristics of the included animal studies

| Study id; author; Year and country of study | Study population | Intervention | Control | Observation Time | Outcomes |
|-------------------------------------------|------------------|--------------|---------|-----------------|----------|
| ÖZAYDIN 2018 [26]; Swiss                  | non-diabetic (Group ND) and diabetic (Group D) groups, each consisting of 36 mice, which were divided into two sub-groups: Insulin (ND/D, n = 18) and Control (Group NDC/DC, n = 18) group. The wounds were 1 cm diameter skin excision. | Insulin ointment (5 IU/g) was administered to DI group and NDI group. | NS ointment (5 mL isotonic NaCl) and 95 g petroleum jelly) to DC group and NDC group. | At 7th and 14th days | Topical insulin application significantly accelerated healing in the treatment of diabetic and non-diabetic wounds with tissue loss in mice. |
| Negrini 2017 [25]; Spain                 | Forty-four healthy adult trachemys scripta elegans (female) were distributed in two groups: Group 1, with 24 animals; Group 2, with 20 animals. One wound was made on the dorsal aspect of each rear limb. | Porcine insulin (40 IU/mL) at 5 IU/mL diluted in glycerol was administered topically 6 h after wound induction and daily during the first week post-injury. | Glycerol (5 IU/mL) was applied topically 6 h after wound induction and daily during the first week post-injury. | At 2, 7, 14, 21 and 28 days | Topical insulin modified the inflammatory response and promoted wound healing. |
| Li CF 2015 [11]; China                   | Two full-thickness 7-mm punch wounds (excision of the skin) were made on the back of the diabetic mice at symmetric sites. | Human isophane insulin suspension (Humulin N, Lilly, Hutchinson, KS; 0.1 U/20 μL saline) were dropped into the wounds every day | Saline (20 μL) were dropped into the wounds every day | At days 1, 3, 5, 9, 11 and 13 | Topical insulin accelerated microvascular maturation and promoted wound healing ratio. |
| BAIRY 2014 [23]; India                  | This study was conducted using six groups of Wistar strain adult rats of either sex (n = 6). First three groups were non-diabetic (ND) rats and the other three had diabetic (D) rats. Circular wounds of 300 mm² on the back of rats. | 0.1 U of regular insulin was applied on edge of wound area twice daily | Normal saline (1 mL/kg/day) twice daily | At days 1, 3, 5, 7, 9, 11, 13, 15, 17 and 19 | Topical insulin enhanced the burn wound healing by shortening the time needed for complete epithelialization. |
| Mate 2014 [24]; India                   | Albino Wistar Rats were divided into 6 groups (n = 6). Group 1 were non-diabetic (ND) rats, and the other group were diabetic rats (D). The excision wound was 1 × 1 cm on the depilated back of the rats. | Insulin was instilled into the wound topically in the dose of 1 U/100 gm² | No treatment | At days 4, 8, 12 and 16 | Topical insulin was safe and accelerated the wound contraction. |
| Lima 2012 [21]; Brazil                  | Six-week-old male Wistar rats were divided into six groups (n = 20). First three groups were non-diabetic (ND) rats and the other three had diabetic (D) rats. A full-thickness excision wound (4.064 mm²) was made to the level of the epidermis and dermis. | 0.5 U/100 g insulin cream daily | Cream with placebo daily | At days 4 and 8 | Topical insulin reduced the wound healing time of diabetic rats. |
| Chen XL 2012 [22]; China                | 42 mice (SPF C57BL/6J; 21 female and 21 male) gender was randomly assigned to control or insulin treatment group. Six full-thickness wounds on the top, middle, and bottom areas of the dorsal skin, 3 at each side symmetrically. | 0.03-U insulin in 20-μL saline was applied once every day | 20-μL saline immediately was applied once every day | At days 1, 2, 3, 5 and 7 | Topical insulin improved epithelization, collagen remodeling and reduce the wound healing times, promote healing rates. |
| Liu Y 2009 [20]; The USA                | 7 mm diameter excision wounds were performed on the back of C57BL/6J mice | 0.03 U of insulin | 30-μL saline solution | At days 1, 2, 3, 5, 7, 9 and 11 | Topical insulin accelerates re-epithelialization and stimulates “maturation” of the healing tissue. |
| Greenway 1999 [16]; The USA             | Six rats (weights 80–120 g) were shaved on the back and a standardised cut was made. | Regular insulin (Iletin-II, which contains 0.01–0.04 mg/mL zinc) three times a day | Saline three times a day | About 9 days | Topical insulin decreased the wound healing time. |
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Grading the evidence

Wound healing rate (clinical)

Two studies compared the effectiveness of local insulin and normal saline based on the healing rate of 75 patients, and the assessment was performed to support the treatment of topical insulin (Fig. 4b).

Discussion

This present study was a systemic review of the complications of the effectiveness of topical insulin used in wound healing in animals and clinical researches. We obtained 13 suitable studies, including nine animal studies and four clinical studies.

Wound healing is a particular mechanism of cascading cellular functions and is made up of three sequential and overlapping stages, including hemostasis and inflammation, proliferation or fibroplasia, and remodeling or maturation stages. The dysfunction of any of these phases could cause improper wound healing [27-30]. However, diabetes can influence the normal wound healing process [31]. Diabetic wound healing is distinguished by delayed cell infiltration and granulation tissue formation, and the epithelialization time of diabetic wounds may be prolonged [32].

The quantitative synthesis determined the following important results: topical insulin can decrease wound healing time and wound area, promoting a percentage of wound contraction in animal studies, whereas in clinical studies, topical insulin can also decrease the time of

Table 2 Summary of key characteristics of the included clinical studies

| Study id; author; Year and country of study | Study population | Intervention | Control | Observation Time | Outcomes |
|-------------------------------------------|------------------|--------------|---------|-----------------|----------|
| Dawoud 2019 [19]; Egypt                   | Patients with chronic wounds in different parts of the body, age between 21 to 75 years, are included in the study. Patients excluded from the study are those who have severe infection, uncontrolled wound bleeding, smokers, patients with immunosuppression, cardiovascular diseases, or any chronic debilitating disease that might affect the outcome of the study. | Insulin-loaded liposomal chitosan gel was applied once daily, left to dry for 30 min, and covered with sterile cotton gauze. | Liposomal chitosan gel without adding insulin was applied once daily, left to dry for 30 min, and covered with sterile cotton gauze. | 2 months | Topical insulin promoted wound healing rate without hypoglycemia, and reduced erythema scale as well as wound area. |
| Atia 2014 [18]; Egypt                     | Patients with acute wounds (burns or crush wounds) or chronic wounds (pressure ulcer) were included. Patients whose age >75 years, smokers, and with immunosuppression, cardiovascular diseases, diabetes mellitus, any chronic debilitating disease, low serum zinc level, complicated wounds, history of abnormal scar formation and/or previous or current medications were excluded. | 1 unit (0.1 mL) of regular insulin for per cm² of wound twice a day | Sterile 0.9% saline twice a day | Unclear | Topical insulin promoted wound healing rate without hypoglycemia. |
| Rezvani 2009 [17]; Iran                   | Patients with acute or chronic wounds in the lower limb extremity were included. Patients with either acute wounds such as crush or burns or chronic wounds such as pressure ulcers in either upper or lower extremities were included. Those with uncontrolled bleeding from the wounds, immunodeficiency, age above 75 years or with diabetes mellitus were excluded. | 10 units (0.1 mL) of insulin crystal for each 10 cm² of wound twice a day | 0.9% sodium chloride solution twice a day | About 45 days | Topical insulin effectively reduced the time for complete wound healing and promoted the healing rate. |
| Greenway 1999 [16]; The United States of America | Five diabetic and six non-diabetic subjects participated in the trial. A standardised wound (skin excision 5 mm long and 1 mm deep) was made on each forearm. The width of the cuts was variable due to separation of the wound edges, a function of skin elasticity. | U-100 Iletin-II regular pork insulin one drop was applied to the wound four times a day | 0.9% sodium chloride four times a day | About 9 days | Topical insulin accelerated wound healing and increased wound healing rate. |
wound healing and increase the healing rate. In both animal and clinical experiments, local insulin has a positive effect on the wound. Insulin is divided into two types in form: liquid and lotion. In animal studies, the main insulins used were as follows: Insulin ointment (5 IU/g), Porcine insulin (40 IU/mL), Human isophane insulin suspension (0.1 U/20 μL saline), regular insulin (0.1 U), insulin (1 U/100 gm²), insulin cream (0.5 U/100 g), insulin (0.03-U/20-μL saline), insulin (0.03 U), regular insulin (contains 0.01–0.04 mg/mL zinc). While in clinical studies, the main insulins used were as follows: Insulin loaded liposomal chitosan gel, regular insulin (1 U/0.1 mL), insulin crystal (10 U/0.1 mL), U-100 Iletin-II regular pork insulin. The application of local insulin also varies in healing time for different types of wounds. In animal experiments, the main types of wounds were: skin excision (1 cm or 7 mm diameter), punch wounds (7 mm), Circular wounds (300 mm²), wound (1 × 1 cm), a full-thickness excision wound (4.064 mm) and skin excision (5 mm long and 1 mm deep). The treatment periods were between one week and one month. While in animal experiments, the main types of wounds were: chronic wounds (pressure ulcer), acute wounds (burns or crush wounds) and skin excision 5 mm long and 1 mm deep in forearm. The treatment periods were between one week and two months, which was longer than in the animal studies.

These literatures support the functions of insulin in promoting wound healing through the following mechanisms of action. Liu et al. [20] indicated that topical insulin expedites re-epithelialization and promotes “maturation” of the healing tissue when applied to skin excision wounds. These effects rely on the insulin receptor, and PI3K-Akt-Rac1 signaling pathways, which stimulate keratinocyte migration, are critically involved and stimulate keratinocytes to produce integrin-α3 and LN332, and cell migration in vitro and in vivo rely on these molecules. Their data also showed that insulin works by stimulating insulin-like growth factor (IGF) 1 receptors. Ghahary et al. [33] illustrated that IGF-1 induces transforming growth factor-beta in dermal fibroblasts conducing to wound healing. Rezvani et al. [17] believed that IGF and insulin have the same molecular structure, especially IGF-1, which acts as a growth factor. According to the report, diabetic wounds have increased neutrophils and lengthened neutrophil infiltration [34]. Hence, injured patients with diabetes suffer from more infectious wounds and prolonged recovery times. Chen et al. [22] suggested that the inflammatory response in the wounded area by restraining wound neutrophil infiltration could be adjusted by topical insulin through the inhibition of chemokine macrophage inflammatory protein-2 (MIP-2) expression. They also found that insulin enhanced neutrophil functions, which indicates that insulin has a certain regulating effect on wound inflammation response in the process of healing. Negrini et al. [25] considered that the view of Chen et al. [22] was contradictory because early infiltration of neutrophils is a vital, first step of the healing course, and the improved healing was put down to an insulin-induced enhanced function of mice neutrophils. They also proved that, at early phases of wound healing, insulin accelerates healing through adjusting wound inflammatory response, especially the number and activity of macrophages, hematrophils, and fibroblasts. Neovascularization is critical for successful wound healing [35]. Data on the topical action of insulin manifest that insulin initially irritates local angiogenesis; therefore, it provides an advantageous environment for wound healing [36-40]. Martínez-Jiménez et al. [41] demonstrated that topical insulin stimulates the formation of blood vessels and advances fibrosis. Li et al. [11] suggested that insulin facilitates vascular maturation during wound healing by improving the expression of α-smooth muscle actin (α-SMA) and platelet-derived growth factor-B (PDGFR-β) and inducing an enhanced expression of angiopoietin-1 (Ang-1), which may be related to the mechanisms of insulin-induced wound healing. The main function of Ang-1 reported might depend on its antiapoptotic effect on endothelial cells in the plastic stage; hence, it may only play an indirect part in the maturation of vessel [42]. ÖZAYDIN et al. [26] found that the topical application

**Fig. 2** Summary of risk of bias of the included animal studies (a) and clinical studies (b)

Low risk of bias: green color; unclear risk of bias: yellow color; high risk of bias: red color.
of NPH insulin, which was used in an ointment form, plays a positive role in the healing of complex wounds with tissue loss, formation of granulation tissue, and epithelization due to faster completion of all stages of the healing course in open wounds.

Although many researches have shown that topical use of insulin can promote wound healing, further study is still needed on the following issues: first, randomized

Fig. 3  Forest plot of wound healing time (a), percentage of wound contraction (b) and wound area (c) between the animal study groups.

a: Topical insulin dramatically reduced the overall wound healing time when compared to normal saline, however, the sub-group analyses were not significant in diabetic and non-diabetic animals.

b: Topical insulin significantly improved the percentage of overall wound contraction when compared to control group, additionally, the sub-group analyses between diabetic animals and non-diabetic animals were also significant.

c: There had significant difference in the overall wound area between the study groups, and the sub-group analyses between diabetic animals and non-diabetic animals also had significance.
Fig. 4 Forest plot of wound healing time (a) and wound healing rate (b) between the clinical study groups

a: The overall wound healing time was greatly reduced when compared with normal saline. But the sub-group analyses are not significant in diabetic and non-diabetic patients.
b: Topical insulin significantly increased the percentage of wound contraction between the two study groups.

Table 3 Summary of findings table as per GRADE working group

| Outcomes                  | Parameters compared                                                                 | No of Participants (studies) | Quality of the evidence (GRADE) | Comments                        |
|---------------------------|--------------------------------------------------------------------------------------|------------------------------|--------------------------------|---------------------------------|
| Wound healing time (animal) | The mean wound healing time in the topical insulin group was 1.27 standard deviations higher (1.75 lower to 0.79 higher) | 86 (five studies)           | ⊗⊗⊗⊖⊖ low¹,²                  | SMD –1.27 (–1.75 to –0.79)     |
| Percentage of wound contraction (animal) | The mean percentage of wound contraction in the topical insulin group was 15.91 standard deviations higher (13.88 lower to 17.95 higher) | 36 (two studies)            | ⊗⊗⊗⊕⊕ low¹,²                  | SMD 15.91 (13.88 to 17.95)     |
| Wound area (animal)       | The mean wound area in the topical insulin group was 19.3 standard deviations higher (21.16 lower to 17.44 higher) | 120 (two studies)           | ⊗⊗⊗⊕⊕ moderate¹               | SMD –19.3 (–21.16 to –17.44)   |
| Wound healing time (clinical) | The mean healing time in the topical insulin group was 2.48 standard deviations higher (3.44 lower to 1.51 higher) | 67 (two studies)            | ⊗⊗⊗⊕⊕ low¹,²                  | SMD –2.48 (–3.44 to –1.51)     |
| Wound healing rate (clinical) | The mean healing time in the topical insulin group was 22.23 standard deviations higher (18.17 lower to 26.28 higher) | 75 (two studies)            | ⊗⊗⊗⊕⊕ low¹,²                  | SMD 22.23 (18.17 to 26.28)     |

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 The measures considered for healing were different in each of the included studies
2 Sample size of the included studies and total sample size were small
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controlled trials should be designed to determine the type of insulin (short-, medium-, or long-acting) and dosages of the insulin in clinical studies; second, the appropriate sample size should be estimated, and a report on all essential elements related to randomization, allocation of concealment, and blindness, and subgroup analysis is also needed for injured patients of different etiologies. Third, the results that help evaluate the efficacy or efficiency of local insulin should be reported in as much detail as possible, such as wound healing rate, wound healing time, wound area, percentage of granulation tissue, microvascular density, and so on. Fourth, it is also necessary to monitor the safety of the experiment and observe the participants’ blood glucose levels during the application of local insulin. There are also some limitations to this present study. The types, usages, and dosages of topical insulin application as well as methods of measuring outcomes used in the included literature are varied. For animal studies, different animal models were used, the size and location of the wounds created were different, and the sample size of some studies was relatively small. For clinical research, the included literature was small, the sample size was small, and the types of wounds were different. Due to limited data, we have not been able to explore and study in detail.

Growth factors are major technological advances of great hope for changing the appearance of wound healing [43-46]. However, growth factors are very expensive and difficult to store for extended periods [47], which is a great economic burden for patients with wounds, especially those with diabetes. However, insulin is inexpensive and easy to buy. A method has been reported to settle the instability as well as uncontrollable release of insulin by formulating it into hydrogels, liposomal chitosan gels, creams, crystals, or ointments, which improved the adherence to the surface of the wound and also enhanced patient’s compliance, especially with painful cuts [17, 19, 21, 26, 29, 48]. Topical application of insulin does not cause hypoglycemia or other side effects [16-19, 41, 49]. It promotes wound healing, shortens the healing process, and reduces medication expenses, duration of treatment, and hospitalization time [26], providing a safe as well as cheap and efficient therapeutic method for acute and chronic wounds, especially for diabetic foot ulcers.

Conclusion

Through analyzing animal studies and RCTs, we have come to a preliminary judgment that the topical application of insulin can aid wound healing. Insulin possesses a great potential in the therapy for chronic and acute wounds. It is believed that with continuous in-depth research on insulin, the mechanism of action of insulin on wounds will become clearer, and insulin will be widely used in the clinical treatment of wound healing.

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Disclosure of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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