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Novel Protamine-Containing Glucomannan Dressing for Improving Wound Healing of Diabetic Full-Thickness Cutaneous Wounds in Mice

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Abstract

Hydrocolloid dressing is the accepted method of wound care. Glucomannan affects skin health by reducing infections, promoting fibroblast accumulation, and stimulating collagen production in cutaneous wounds. Protamine has antibacterial effect and protamine-containing composite materials promote diabetic wound healing. A novel protamine-containing glucomannan dressing was prepared, and its wound-healing effects were compared with those of glucomannan and hydrocolloid dressings. To evaluate the effects of these dressings, full-thickness skin defects were created in nondiabetic, db/db diabetic, and streptozotocin-induced diabetic mice. The wound areas covered with the dressings were measured and compared. In nondiabetic mice, the three types of dressings exhibited no difference in wound-healing effects after day 5. In db/db diabetic mice, protamine-containing glucomannan dressings appeared to be more effective for wound healing than glucomannan dressings; however, no statistically significant difference was noted. Glucomannan and protamine-containing glucomannan dressings demonstrated significantly more effective wound healing than hydrocolloid dressings. In streptozotocin-induced diabetic mice, all mice with hydrocolloid dressings died within 4 days after wounding, whereas those with glucomannan and protamine-containing glucomannan dressings developed scar at 21 days after wounding. Moreover, protamine-containing glucomannan dressings showed significantly more effective wound

healing than glucomannan dressings from day 5 to 15 after wounding. The various effects of protamine likely add to those of glucomannan to promote wound healing. These findings suggested that protamine added to glucomannan dressings may further enhance the wound-healing effect of glucomannan dressings. Although the potential use of protamine-containing glucomannan dressings for the treatment of human skin wounds may be worth exploring, these findings should be interpreted cautiously because the results were derived from animal experiments and histological evaluation was not performed in this study. Further rigorous studies are required before any translational or clinical implications can be drawn.

Keywords

Diabetic Wound, Glucomannan, Protamine, Wound Dressing, Wound Healing

1. Introduction

Proper wound dressing is crucial following skin damage to protect the wound from complications, including infection or further trauma. Moist wound dressing, also known as contemporary wound dressing, is currently the accepted method of wound care. Various polymers have been employed for developing modern wound dressings in the form of films, gels, and foams. These polymers are selected on the basis of the clinical setting's wound bed characteristics, exudate levels, and wound depth, and dressings should be free from toxic agents, non-allergenic, biocompatible, can maintain a moist environment around the wound, and absorb exudates to accelerate wound healing [1]-[3].

Delayed wound healing is a major problem in diabetes, and the development of improved wound dressings remains an important challenge in diabetic wound care. Diabetic wounds are characterized by prolonged inflammation and impaired tissue repair, resulting in delayed healing and increased risk of complications [4].

We obtained a novel dressing comprising glucomannan and protamine from Umios Corporation (Tokyo, Japan). Glucomannan-based materials have already been reported to be beneficial for wound healing. Glucomannan (mannan-containing carbohydrates) positively affects skin health by reducing infections, promoting fibroblast accumulation, and stimulating collagen production in cutaneous wounds [5]-[7]. Protamine is extracted from the sperm cells of vertebrates and contains an arginine-rich polycationic protein; biocompatibility testing in animals revealed that protamine is highly safe for use in live organisms and has antibacterial activity [8] [9]. Moreover, protamine-containing composite materials have shown beneficial effects on diabetic wound healing [10]. We compared the cutaneous wound-healing effects of three wound dressings, including this novel protamine-containing wound dressing, glucomannan wound dressing, and hydrocolloid dressing, on diabetic mice. The glucomannan wound dressing did not contain

protamine. The hydrocolloid dressing was purchased from 3M Health Care (Tegaderm, Tokyo, Japan), which we and several researchers used for cutaneous wound healing [11]. Diabetic mice have been used as animal models for chronic wound healing in humans as the wound healing is delayed owing to several factors, including prolonged inflammatory stage and delayed proliferation and remodeling stages [12] [13]. We used db/db mice (C57BLKS/J Iar- + Lepr^{db}/ + Lepr^{db}) as a type-2 diabetic model and streptozotocin (STZ)-induced diabetic mice as a type-1 diabetic model.

Considering the role of protamine in wound healing, this study aimed to analyze whether a protamine-containing dressing promotes the healing of full-thickness skin defects created in the mice under nondiabetic or diabetic conditions.

2. Materials and Methods

2.1. Animals

Mice were purchased at the same age and were randomly assigned to the experimental groups on the day of arrival. Fifteen healthy 7 - 8-week-old male C57BL/6J mice with normal blood glucose levels were used and regarded as nondiabetic mice (DM-mice). Furthermore, fifteen 7 - 8-week-old male db/db mice (C57BLKS/J Iar- + Lepr^{db}/ + Lepr^{db}) as a type-2 diabetic model (Sankyo Lab Service Co., Tokyo, Japan) were used and considered as db/db diabetic mice (db/dbDM + mice). Moreover, 15 STZ-induced male C57BL/6J mice aged 7 - 8 weeks old as a type-1 diabetic model according to the method by [14] were used and regarded as STZDM + mice. Mice with blood glucose levels > 400 mg/dL at 1 day following intraperitoneal injection of STZ (100 mg/kg weight) were used. The nonfasting blood glucose levels of nondiabetic and diabetic mice were assessed using a glucose rapid test stick (Nipro CareFast R; Nipro, Osaka, Japan). Blood samples for blood glucose level assessment were obtained by creating a small prick on each mouse's tail before wounding.

Animals were maintained and individually caged in a temperature-controlled room (25.0˚C ± 2.0˚C) with 12 h of light and dark cycle (12 h/12 h) and free access to water and chow for the entire experimental period. The experiments conducted in this study were reviewed and approved by the Animal Experiment and Use Committee of Kanazawa University and performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of Kanazawa University, Japan (AP-204122).

2.2. Wound Dressings

We used the following three types of wound dressings: hydrocolloid dressing (Tegaderm; 3M Health Care, Tokyo, Japan) (Hyd), glucomannan dressing mixed with protamine (Prot+), and glucomannan dressing without protamine (Prot−) (**Figure 1**). The hydrocolloid dressing consisted of a inner layer of hydrocolloid adhesive and an outer film layer [15]. Prot+ is a mixture of glucomannan (95%) and protamine (5%) (30-μm thick) on a nonwoven fabric (1.8-mm thick), whereas

Prot− comprises only glucomannan (30-μm thick) on a nonwoven fabric (1.8-mm thick). These dressings were provided by Umios Corporation (Tokyo, Japan). Glucomannan wound dressings are a patented invention (p5473387 in Japan) and are commercialized under the name Hydro Help (Toyo Kagaku INC, Japan).

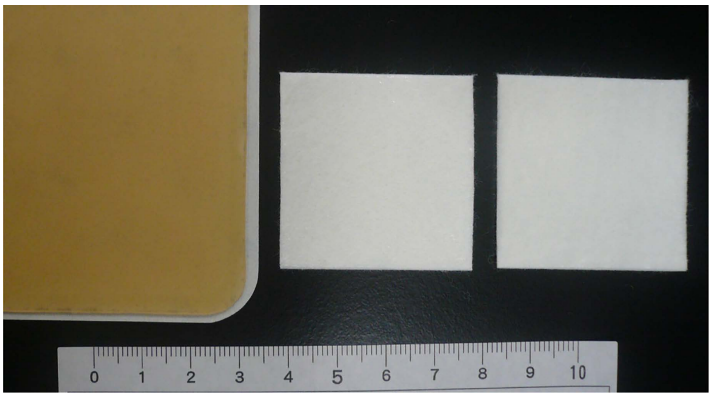

Figure 1. Hydrocolloid, glucomannan, and glucomannan mixed with protamine dressings (from left to right).

2.3. Wounding and Treatment

Before the wounding day, dorsal parts of the mice were shaved under inhalational anesthesia with 1.5% isoflurane (Wako, Tokyo, Japan) at 1.5 L O_2/min connected to an acrylic box. Mice were divided into the following nine groups (n = 5 mice/group): nondiabetic mice treated with the hydrocolloid dressing (DM-Hyd), nondiabetic mice treated with the protamine-containing glucomannan dressing (DM-Prot+), nondiabetic mice treated with the glucomannan dressing without protamine (DM-Prot−), db/db mice treated with the hydrocolloid dressing (db/dbDM + Hyd), db/db mice treated with the protamine-containing glucomannan dressing (db/dbDM + Prot+), db/db mice treated with the glucomannan dressing without protamine (db/dbDM + Prot−), STZ-induced mice treated with the hydrocolloid dressing (STZDM + Hyd), STZ-induced mice treated with the protamine-containing glucomannan dressing (STZDM + Prot+), and STZ-induced mice treated with the glucomannan dressing without protamine (STZDM + Prot−).

On the wounding day, under inhalational anesthesia, the weights of the mice were measured, the dorsal portions were subsequently disinfected with 70% ethanol, and two circular full-thickness cutaneous wounds (4-mm diameter), including the panniculus carnosus muscle, were created on both sides of the dorsal portion using a Kai sterile disposable biopsy punch (Kai Industries Co., Ltd., Gifu, Japan). Wounds were covered by dressings based on the abovementioned nine mice groups and wrapped with sticky bandages (Skinergate™; Nichiban, Tokyo, Japan), which were replaced daily according to previous studies by Mukai *et al.* [16] [17].

2.4. Wound Observations

Wounding day was designated as day 0. The wound healing progression was monitored daily until days 14 (nondiabetic mice) and 21 (diabetic mice) under inha-

lational anesthesia. The weights of the mice were measured daily from day 0 to day 14 or 21 after wounding. Dressing changes, wound tracing, and wound area measurements were performed using the same standardized procedures across all groups. During dressing changes, the skin surrounding the wound was gently held while the dressing and tape were removed to minimize mechanical stress on the wound. The edges of each wound were monitored daily by drawing the wound area pattern on a polypropylene sheet using a permanent marker, and images of the wounds were taken. Traces on the sheets were captured using a scanner onto a personal computer using Adobe Photoshop Elements 11.0 (Adobe System Inc., Tokyo, Japan), and wound areas were measured using ImageJ image analysis software (National Institutes of Health, Bethesda, MD, USA). The wound area was expressed as the daily ratio of the wound area compared with the initial wound area on day 0 when the wound was created according to previous studies [16] [17]. Humane endpoints included difficulty in food or water intake, decreased activity, and persistent recumbency or crouching. Mice meeting these criteria were to be carefully monitored and handled in accordance with the animal experimental guidelines.

2.5. Statistical Analysis

Data were presented as means ± standard deviations. For wound-area analysis, the two wounds in each mouse were averaged to obtain a single mean wound-area value per mouse, and this mouse-level value was used as the experimental unit. Mean comparisons across the groups were performed using one-way analysis of variance, followed by post-hoc pairwise comparisons using the Tukey-Kramer multiple comparison test, and/or using a paired t-test, with SPSS 25.0 (SPSS Inc., Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

3. Results

3.1. Animals

All DM-groups survived until day 14 after wounding. All db/dbDM + groups survived until day 21 after wounding. Conversely, all mice in the STZDM + Hyd group died at 4 days after wounding; however, those in the STZDM + Prot+ and STZDM + Prt− group survived until day 21 after wounding.

The weights of the DM-groups on day 0 before wounding and day 14 after wounding were approximately 21 - 23 and 22 - 24 g, respectively (**Table 1**). The weights of the db/dbDM + groups on day 0 before wounding and day 21 after wounding were approximately 41 - 46 and 37 - 40 g, respectively. The weights of the STZDM + groups on day 0 before wounding and day 21 after wounding were approximately 21 - 22 and 17 - 20 g, respectively. The STZDM + groups exhibited lower weights than the DM- and db/dbDM + groups.

The blood glucose levels of the DM-groups on day 0 before wounding and day 14 after wounding were approximately 110 - 120 and 100 - 130 mg/dL, respectively (**Table 2**). The blood glucose levels of the db/dbDM + groups on day 0 before

wounding and day 21 after wounding were approximately 452 - 573 and 412 - 600 mg/dL, respectively. The blood glucose levels of the STZDM + groups on day 0 before wounding and day 14 after wounding were approximately 480 - 600 and 490 - 600 mg/dL, respectively. The STZDM + groups demonstrated higher blood glucose levels than the DM- and db/dbDM + groups.

Table 1. Weights (g) of the mice in all groups.

Group	Day 0 before wounding	Day 14 after wounding
DM-Hyd	22.3 ± 1.7	23.2 ± 1.6
DM-Prot+	21.8 ± 0.2	23.1 ± 0.7
DM-Prot−	23.3 ± 0.1	23.1 ± 0.3
	Day 0	**Day 21**
db/dbDM + Hyd	42.5 ± 1.6	38.4 ± 3.5
db/dbDM + Prot+	41.8 ± 1.1	41.1 ± 2.3
db/dbDM + Prot−	41.8 ± 1.8	38.0 ± 3.5
	Day 0	**Day 21**
STZDM + Hyd	19.9 ± 1.3	Died
STZDM + Prot+	22.6 ± 0.1	19.0 ± 1.3
STZDM + Prot−	22.3 ± 0.5	20.4 ± 0.8

Table 2. Blood glucose levels (mg/dL) of the mice in all groups.

Group	Day 0 before wounding	Day 14 after wounding
DM-Hyd	119.8 ± 11.3	118.2 ± 11.3
DM-Prot+	112.8 ± 13.0	125.4 ± 7.0
DM-Prot−	119.0 ± 14.7	127.0 ± 5.4
	Day 0	**Day 21**
db/dbDM + Hyd	513.3 ± 49.4	494.6 ± 78.9
db/dbDM + Prot+	529.6 ± 75.6	601.0 ± 0.0
db/dbDM + Prot−	576.6 ± 15.4	601.0 ± 0.0
	Day 0	**Day 21**
STZDM + Hyd	561.2 ± 46.9	Died
STZDM + Prot+	574.8 ± 43.5	563.2 ± 48.0
STZDM + Prot−	562.8 ± 39.8	584.4 ± 24.4

3.2. Wound Dressings Absorbed Exudates

The hydrocolloid dressings of the DM-Hyd group on days 1 and 7 after wounding were markedly swollen from absorbing exudates. As the former were larger than the latter, the amount of exudates decreased from days 1 to 7 after wounding. The dressings of the DM-Prot+ group on day 1 after wounding absorbed a tiny bit of exudates; therefore, determining whether the dressings were wet by touching them was challenging, similar to the dressings of the DM-Prot− group. On day 7 after wounding, both dressings of the DM-Prot+ and DM-Prot− groups were almost dry and not wet when touched.

The hydrocolloid dressings of the db/dbDM + Hyd group on days 7 and 14 after wounding were evidently swollen from absorbing exudates. The dressings of the db/dbDM + Prot+ group on day 7 after wounding absorbed a tiny bit of exudates; therefore, determining whether the dressings were wet by touching them was challenging, similar to the dressings of the db/dbDM + Prot− group. On day 14 after wounding, the db/dbDM + Prot+ and db/dbDM + Prot− groups were almost very dry and not wet when touched.

On days 1 and 4 after wounding, the hydrocolloid dressings of the STZDM + Hyd group were noticeably swollen from absorbing exudates. The dressings of the STZDM + Prot+ and STZDM + Prot− groups on day 1 after wounding absorbed a tiny bit of exudates. On day 7 after wounding, both dressings of the STZDM + Prot+ and STZDM + Prot− groups were almost very dry and not wet when touched (Figure 2).

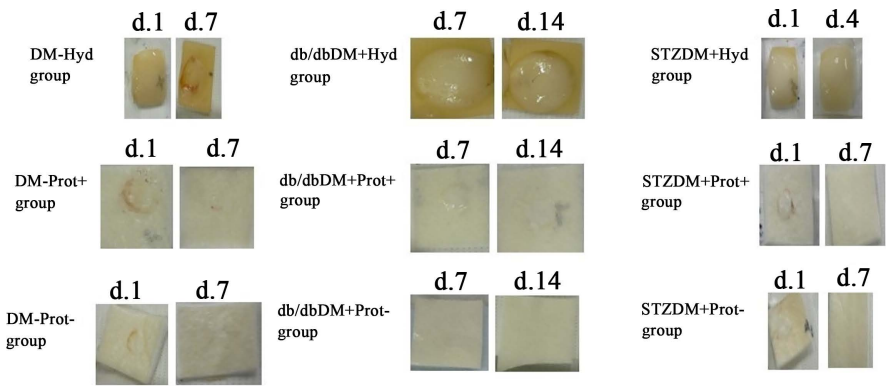

Figure 2. Exudate absorption on wound dressing. Note that hydrocolloid dressings (Hyd) absorb a larger amount of exudates than dressings composed of glucomannan and protamine (Prot+) and dressings composed of glucomannan (Prot−). d indicates the day after wounding.

3.3. Wound Assessment and Measurement

In the DM-Hyd group, the wound areas expanded and exceeded the initial size until day 4, and started to become smaller compared with the initial wound area; subsequently, the areas gradually decreased until day 14 (Figure 3). In the DM-Prot+ group, the ratio of the wound areas decreased starting on day 1 (0.81 ± 0.14) and continued to decrease, almost closed, on day 14 (0.06 ± 0.05). In the DM-

Prot− group, decreased wound area ratios were noted since day 1 (0.77 ± 0.18), with comparable wound areas on days 2 and 3 compared with those in the DM-Prot+ group. The wound continuously decreased in size until almost closed on day 14 (0.06 ± 0.05). Furthermore, the DM-Hyd group demonstrated significantly larger wound area ratios than the DM-Prot+ and DM-Prot− groups on days 1 - 4 ($p < 0.05$) (**Figure 4(A)**). No significant differences were observed between the DM-Prot+ and DM-Prot− groups were noted during all observation days; however, the DM-Prot+ group exhibited a smaller wound are ratio than the DM-Prot− group.

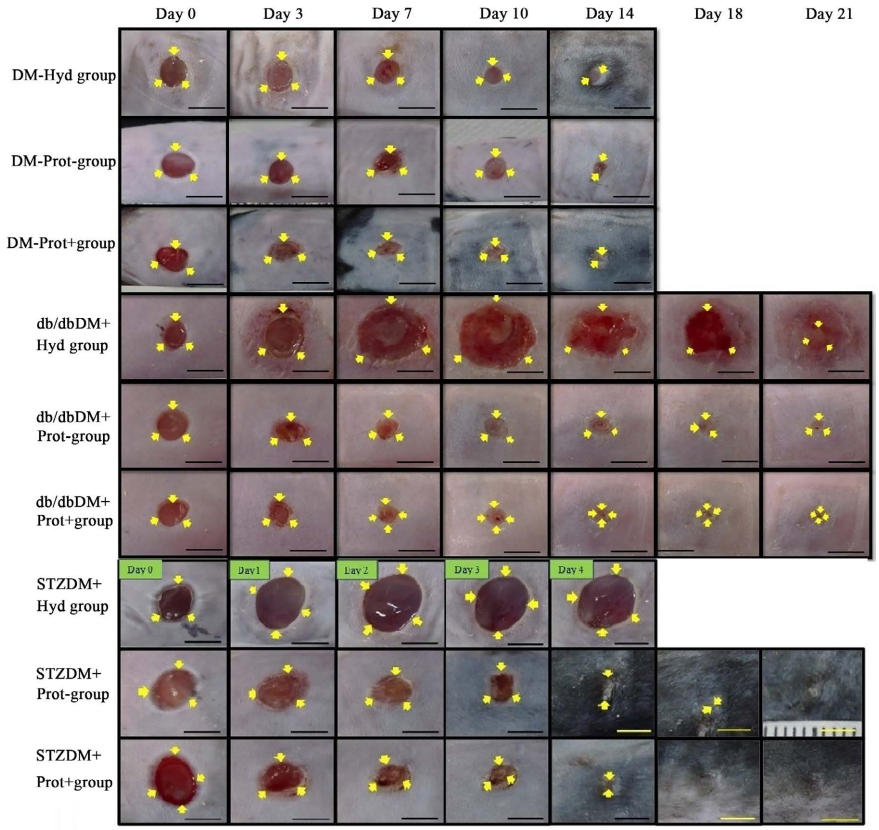

Figure 3. Wound images of each group and the day after wounding. The STZDM + Hyd group shows wounds only from days 0 to 4 after wounding as all mice in this group survived only until day 4. Arrows indicate wound edges. Bar: 5 mm.

The wound areas in the db/dbDM + Hyd group dramatically increased until day 9 (6.18 ± 1.32) and subsequently decreased until day 21; however, the wound area remained larger than the initial wound area (1.71 ± 1.25) (**Figure 3** and **Figure 4(B)**). In the db/dbDM + Prot+ group, the wound area immediately decreased from day 1 of observation (0.91 ± 0.14) and continued decreasing until day 21 (0.32 ± 0.08), forming small scars. In the db/dbDM + Prot− group, the wound area slightly increased until day 2 (1.05 ± 0.19) and subsequently decreased and became smaller than the initial wound area on day 3 (0.94 ± 0.18). The db/dbDM + Hyd group showed a significantly higher wound area ratio than the db/dbDM + Prot+ and db/dbDM + Prot− groups on all observation days ($p < 0.01$) (**Figure**

4(B)). In general, the db/dbDM + Prot+ group demonstrated smaller daily wound area ratios than the db/dbDM + Prot− group until day 21; however, no statistical differences were noted between the two groups.

In the STZDM + Hyd group, wherein all mice died until day 4 after wounding, the wound area dramatically increased to approximately 2.5-fold larger on day 4 than that on day 0 (Figure 3 and Figure 4(C)). Conversely, in the STZDM + Prot+ and STZDM + Prot− groups, the wound areas gradually decreased from days 1 - 21 after wounding and eventually forming small scars. Statistical differences were noted between the STZDM + Prot+ and STZDM + Prot− groups from days 5 to 15 after wounding ($p < 0.05$) (Figure 4(C)).

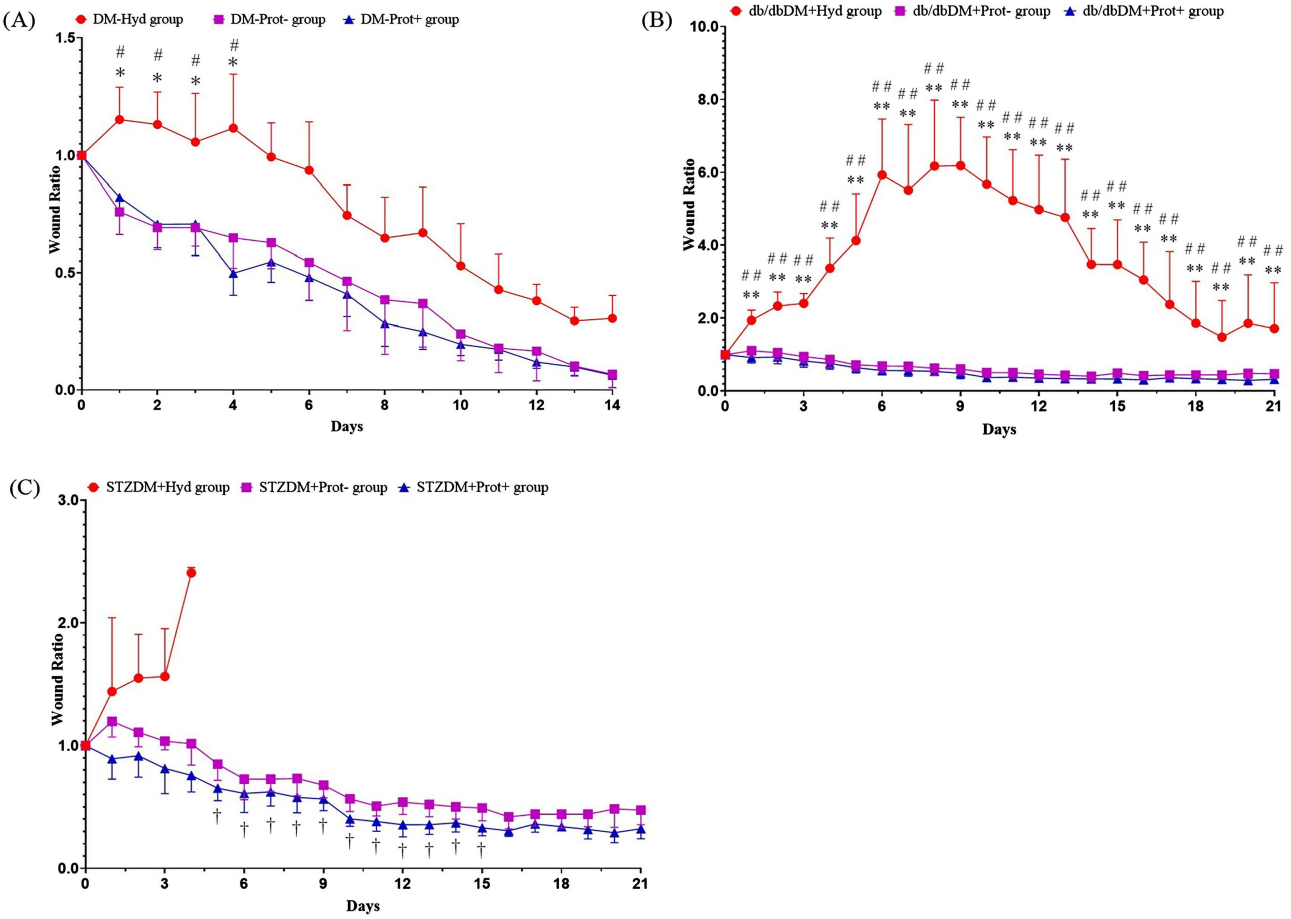

Figure 4. Comparison of wound area ratios between normal and diabetic mice. The ratios of wound areas to the initial area on day 0 are shown as line graphs for each day. (A) The wound area ratio in the DM-group is expressed as means ± standard deviations (SDs), ANOVA, Tukey-Kramer; $^{*}p < 0.05$, Hyd vs Prot−; $^{\#}p < 0.05$, Hyd vs Prot+. (B) the wound area ratio in the DM + group is expressed as means ± SDs, ANOVA, Tukey-Kramer; $^{**}p < 0.01$, Hyd vs Prot−; $^{\#\#}p < 0.01$, Hyd vs Prot+. (C) the wound area ratio in the STZ group. The STZDM + Hyd group is only from days 0 to 4 after wounding as all mice in this group survived only until day 4. Values are expressed as means ± SDs, ANOVA, Tukey-Kramer; $^{\dagger}p < 0.05$, Prot− vs Prot+.

4. Discussion

Diabetic wound healing remains a major challenge because diabetes is associated with delayed wound closure and impaired tissue repair. Glucomannan-based ma-

terials have been reported to support wound healing [5]-[7]. However, the wound-healing effects of a protamine-containing glucomannan dressing have not been sufficiently evaluated, particularly across different diabetic wound models. In this context, the novelty of the present study lies in the comparative evaluation of a protamine-containing glucomannan dressing, a glucomannan dressing without protamine, and a hydrocolloid dressing in both STZ-induced diabetic mice and db/db mice. Its scientific contribution is that it provides comparative preclinical data on dressing performance in two distinct diabetic wound models and suggests the potential utility of protamine-containing glucomannan dressings in delayed wound healing.

This study revealed the following findings: 1) glucomannan and protamine-containing glucomannan dressings were better than the hydrocolloid dressing used in this study for wound dressing in mice, 2) the hydrocolloid dressing used in this study did not appear to be a suitable wound dressing for diabetic mice, and 3) the protamine-containing glucomannan dressing showed a significantly greater wound-healing effect than the glucomannan dressing in STZ-induced diabetic mice.

Hydrocolloid dressings are frequently used for human cutaneous wounds and have been demonstrated to be effective [2] [3]. Moreover, they are frequently used in animal cutaneous wound experiments. Previous experiments on nondiabetic mice revealed that applying a hydrocolloid dressing expanded the wound area initially during the inflammatory phase (several days after creating the wound) and subsequently gradually decreased in size until the wound became a scar [16]-[18]. However, cutaneous wound experiments on db/db mice demonstrated that covering the wounds with hydrocolloid dressing did not shrink the wound area, significantly delaying wound healing [13] [19]. In the present study, wound healing in the db/dbDM + Hyd group progressed less favorably than that in the db/dbDM + Prot+ and db/dbDM + Prot− groups. In addition, all mice in the STZDM + Hyd group died by day 4 after wounding, whereas the wounds in the STZDM + Prot+ and STZDM + Prot− groups shrank and developed into scars. These findings suggest that, under the conditions of this study, the glucomannan and protamine-containing glucomannan dressings were more suitable wound dressings for mice than the hydrocolloid dressing used in this study. This finding aligns with our previous studies, which also reported that the hydrocolloid dressing delayed cutaneous wound healing in db/db mice by increasing the wound area size [1] [13] [19]. However, this comparison should be interpreted with caution because the dressings compared in this study differed not only in composition but also in structure and absorbency-related properties. Therefore, the hydrocolloid-versus-glucomannan findings in this study should be limited to the specific dressing systems tested.

In addition to wound enlargement, marked swelling of the dressing associated with abundant exudate were observed in the hydrocolloid dressing group. In the db/dbDM + Hyd and STZDM + Hyd groups, the hydrocolloid dressings were ev-

idently swollen after wounding, suggesting absorption of a relatively large amount of exudate. In contrast, the dressings in the db/dbDM + Prot+, db/dbDM + Prot−, STZDM + Prot+, and STZDM + Prot− groups absorbed little exudate and were almost dry by day 14 after wounding. These findings suggest that the hydrocolloid dressing used in this study may not have been suitable for diabetic mice because it appeared to absorb a large amount of exudate. With regard to the deaths in the STZDM + Hyd group at day 4 after wounding, the direct cause of death remains unknown because we did not anticipate these deaths and did not obtain objective physiological, pathological, or biochemical data to determine the cause. Therefore, the results of this experiment indicate that careful selection of wound dressings is crucial in animal studies on cutaneous wound healing.

Previous studies have shown that glucomannan has wound-healing properties, including effects on fibroblast migration and proliferation, extracellular matrix production, and modulation of inflammatory responses [5]-[7]. Protamine has also been reported to have antimicrobial activity [8] [9] and protamine-containing composite materials to promote wound healing [10]. In the present study, the protamine-containing glucomannan dressing showed a significantly greater wound-healing effect than the glucomannan dressing in STZ-induced diabetic mice, whereas no significant difference was observed in db/db mice. Although the reason for this difference remains unclear because no histological or other mechanistic evaluations were performed in this study, the smaller wound area observed in the STZDM + Prot+ group suggests a possible beneficial effect of protamine addition in STZ-induced diabetic mice.

This study is limited by its relatively small sample size, which may have reduced statistical power. Therefore, the findings should be interpreted cautiously, and larger confirmatory studies are warranted. In addition, because a protamine-only group was not included and no histological or biochemical analyses were performed, the specific contribution of protamine and the underlying mechanisms could not be fully clarified. Moreover, the study primarily relied on gross wound-area measurements and did not include histological or mechanistic evaluations, such as assessments of inflammatory responses, angiogenesis, collagen deposition, and re-epithelialization. Therefore, the mechanisms underlying the observed wound-healing effects could not be determined. Further studies are needed to evaluate protamine alone and in combination with glucomannan, investigate the mechanisms involved, and confirm the safety and reproducibility of the findings across diabetic models and experimental settings.

5. Conclusion

Glucomannan and protamine-containing glucomannan dressings were more favorable than the hydrocolloid dressing used in this study for wound healing in diabetic mice. Moreover, the protamine-containing glucomannan dressing showed a significantly greater wound-healing effect than the glucomannan dressing in STZ-induced diabetic mice, suggesting a possible added benefit of protamine in

this model. However, because no histological or mechanistic evaluations were performed, the underlying mechanisms remain unclear. These findings should be interpreted cautiously, and further rigorous studies are required before any translational or clinical implications can be drawn.

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Conflicts of Interest

DK and KI are employees of Umios Corporation. Their involvement was limited to developing and providing study materials and financial support. They were not involved in animal allocation, data collection, outcome assessment, data analysis, interpretation of the results, preparation of the manuscript, or the decision to submit the manuscript for publication. All experimental procedures, outcome assessment, data analysis, and interpretation were conducted by the academic investigators.

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