SYSTEMATIC REVIEW

# Comparison of Zinc Chitosan and Silver Dressing in Healing of Diabetic Ulcer: Systematic Review

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## ABSTRACT

**Introduction:** Diabetes mellitus (DM) is one of the non-communicable diseases that can cause the most serious complications such as CHD, cerebrovascular disorders, peripheral arterial disorders, and diabetic foot ulcers. DM can occur due to metabolic disorders caused by the pancreas not being able to produce the amount of insulin needed by the body. Several studies related to DM healing methods can use chitosan and silver dressings. Chitosan as a gelling fiber has an impact on the clinical outcome of chronic wounds which is indicated by reducing wound size, preventing wound holes due to accumulation of exudate. Meanwhile, the use of silver dressings with activated carbon can reduce the wound size and was effective in overcoming excessive exudate, foul odor, pain, and maceration. The obejective was to analyze the effectiveness in the use of Zinc Chitosan Cream and Silver dressing on the healing process of diabetic ulcers. **Methods:** An international electronic database was used as the source of the articles in this systematic review. **Results:** The systematic review showed that the factors that greatly affect wound healing are Chitosan-based materials and silver dressings that aim to kill bacteria in diabetic ulcers so that treatment time can be shorter. **Conclusion:** Zinc Chitosan Cream and Silver dressing can be used for diabetic patients with foot ulcers in the wound healing process using moist treatments. Further research is needed to compare the effectiveness of the diabetic ulcer healing process in type II Diabetes Mellitus patients.

**Keywords:** Diabetic Foot Ulcer, Zinc Chitosan Cream, Silver Bandage

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## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that is caused when the pancreas cannot produce the amount of insulin needed by the body or cannot use insulin efficiently, resulting in an increase in glucose levels in the blood (1). DM is one of the four priority non-communicable diseases that must be followed up by world leaders to find solutions to prevent further complications. Medan city is the capital of North Sumatra Province. It is ranked 7th (10928 people) with the highest recorded DM cases after Binjai, Deli Serdang, Gunung Sitoli, Toba Samosir, Sibolga, Langkat with 1.71% (2). After being diagnosed with DM, it takes 10-15 years to cause macrovascular symptoms in the form of: CHD, cerebrovascular disorders, and peripheral arterial disorders (3). One of the most serious and most common complications caused by diabetes mellitus is diabetic foot ulcers (4).

Chitosan as a gelling fiber has an impact on clinical outcomes of chronic wounds which is indicated by reducing wound size, preventing wound holes due to accumulation of exudate, preventing dehydration of the wound bed, reducing odor and increasing healthy granulation of fragile tissue (5,6,7,8). Chitosan and Nano-zinc oxide (nZnO) are excellent healer because they stimulate homeostasis and accelerate tissue regeneration. Moreover they are widely used because of their non-toxicity, stability, biodegradability, and biocompatibility (9,10).

Based on a previous study on the use of silver dressings, information in a review made by Ravichandran & Chitti (11) stated that doctors have reverted to the use of silver dressings for wound due to the increase in antibiotic-resistant bacteria such as Methicillin-resistant *Staphylococcus aureus*/MRSA. According to the research by Tsang, 2017 (12), the Nanocrystalline silver (nAg) on patients with Type II DM, uninfected wounds, debridement in a control experiment showed a greater wound reduction by 97.45% with a larger but not significant reduction of microorganisms (13). It was seen that the use of hydro cellular foam dressings

with silver and polyacrylate dressings with activated carbon resulted in reduction of wound size and was effective in dealing with excessive exudate, foul odor, pain and maceration caused by wound infection with a frequency of 12 weeks dressings and with the addition of a secondary dressing.

Another research (14) using observational study among 50 cases of diabetic foot patients with silver-based dressings showed that silver-based dressings were effective in wound healing as indicated by 47 cases (94%). This treatment resulted in minimal serous exudate, with healthy granulation of tissue, the absence of micro-organisms and a good healing rate. Another study (15) stated that antimicrobial properties have been used in the preparation of wound dressings. This type of wound care is widely used in practice and shows promising results in the healing of contaminated wounds. A subsequent study (16) showed that using chitosan with silver gave significant results in the reduction of ulcer area among group using chitosan and AgNPs (Silver nanoparticles). In this treatment purulent fluid disappeared, and bacterial cultures became negative. Silver nanoparticles (AgNP) has a strong antimicrobial effect, as it binds to the bacterial wall, enzymes, and DNA.

Another recent study (17) stated that dressings made from alginate, hyaluronan, and Chitlac in membrane form were effective in vitro against both planktonic bacteria and biofilms bacteria. This membrane prevents the formation of bacterial colonization and treats infected wounds. Components of Chitlac-AgNPs (silver nanoparticles) have been proven to inhibit the proteolytic activity of MMPs (Matrix metalloproteinases) in vitro which can cause wounds to heal.

The study's purpose is to identify and analyze a systematic review of previous research using narrative descriptive analysis of some of the main findings of the research article that discusses the application of zinc chitosan cream and silver dressing in healing of diabetic ulcers.

## MATERIALS AND METHODS

### Methods

The writing method used systematic review based on the specific PRISMA diagram guidelines. The author uses PRISMA as a standard in reviewing and selecting research articles. The PRISMA guideline is a form of instrument that aims to assist writers in improving the quality of the selection of research articles in a systematic review which consists of four stages (18).

In addition, the standard in conducting a study or analysis of research articles in this systematic review also uses the PICO model which consists of Population (P), Intervention (I), Comparison (C), and Outcome (O). The PICO model was used by researchers in determining the inclusion and exclusion criteria in this systematic review. The criteria determined by the researcher assisted in selecting research articles.

### Search Information Sources

An international electronic database consisting of ProQuest, EBSCO (CINAHL, MEDLINE), and PubMed as the source of the articles was used in this systematic review with the publication period of research articles starting from 2015 - 2020 (the last 5 years).

### Search Strategy

The search strategy carried out by the author for this systematic review uses several keywords in the search in the database according to the topic and title of the study using the Boolean operator's standard. The keywords used include "Diabetic Ulcer" AND "Zinc Chitosan" AND "Silver" AND "Diabetes Mellitus" AND "Healing".

### Article Selection

The process of selecting research articles by the author for this systematic review uses the PRISMA method with four stages. The first stage is the identification of the stage, the authors combine research articles from all search sources in the database. The second stage is screening, at this stage the author selects titles and research articles that are adjusted to the inclusion criteria and those that are not suitable will be excluded. The third stage is eligibility, at this stage the author makes a selection based on the full text of the research article and still adjusts to the inclusion criteria. The fourth stage is the including stage, articles that have been reviewed in full text and meet the inclusion criteria will enter at this stage, because research articles have been obtained that are truly appropriate and relevant to the topic and title of the research for a systematic review (19).

### Quality Assessment

The quality of writing this systematic review uses the JBI Critical Appraisal guidelines to assess the quality of a research article. JBI Critical Appraisal is an instrument used to assess a methodological quality of a study to determine the extent to which a study has addressed possible biases in its design, intervention and analysis. The JBI Critical Appraisal instrument is also adapted to the type of research used, including the JBI Critical Appraisal for quasy-experiment, JBI Critical Appraisal for Randomized controlled trial, and others (20).

### Data Extraction

The measurement instrument was done using Bates-Jensen Wound Assessment Tools (21). Data was extracted in writing this systematic review to provide information from notes that are tailored to the research objectives. The data extracted from each of the articles that passed the selection based on the PRISMA method consisted of the author, year of publication, the research objectives, the research design, the main findings, the limitations of the study. The results of data extraction

can be seen in the Table I.

**Table I: Inclusion Criteria and Exclusion Criteria**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| The population or sample in the research article focuses on patients Diabetes Type II with diabetic ulcers, chronic wound and stable conditions | The population or sample as patients Diabetes Type I |
| The intervention used in wound care in the research article used primary dressings made of zinc chitosan cream and silver | The intervention not used zinc chitosan cream and silver dressing |
| Outcome measures focused on reducing wound size, epithelizing, and killing bacteria | Outcome measures focused on reducing wound size, epithelizing, and killing bacteria not to patients Diabetes Type II |
| Quasy-experiment, RCT, case study, in vivo in vitro | Qualitative research, cross sectional study, systematic review |
| Articles published in the range of 2015 - 2020 and full text | Articles published before of 2015 |
| Articles in english | Articles not in English |

## RESULTS

The search results of the research articles based on the PRISMA diagram can be seen in the Figure 1, where the identification stage obtained as many as 7.662 articles from several databases used. EBSCO (CINAHL, MEDLINE) as many as 7.243 articles, 51 articles, ProQuest 142 articles and PubMed 226 articles. In the second stage, namely the screening stage, there was a reduction in the number of the same or duplicate articles by 4.567 articles, so that 3.095 articles were reviewed based on the title and abstract of the article. After the selection, 3.070 articles were excluded because the type of research was qualitative, cross sectional, so that it did not fit the inclusion criteria. In the third stage, namely the eligibility stage, a full text review was carried out on 25 articles that met the inclusion criteria, at these stage 18 articles were excluded because outcome measures did not focus on reducing wound size, epithelizing, and killing bacteria, articles not in English and articles published before 2015. In the fourth stage, namely the included stage, 7 articles were obtained based on the selection results and according to the inclusion criteria. For more details, the summary of research article for characteristic zinc chitosan and silver chitosan is shown in Table II.

## DISCUSSION

Approximately 81.6% of ulcers in the gaiter area (between the ankle and calf), had pus and positive bacteria cultures. There was a significant reduction in the ulcer area in the group treated with chitosan and AgNPs (Silver nanoparticles), the purulent fluid disappeared, and the bacterial culture was negative. AgNP has a strong antimicrobial effect, because it binds to the walls of bacteria, enzymes and DNA. Chitosan exhibits strong antifungal properties and bactericidal effects against Gram-positive and Gram-negative. For about 11 of 38 patients (28.95%) who were in the chitosan group showed complete healing and ulcer closure, with no complications (22)

Nano-zinc oxide nZnO / BCM (carboxyl BC membrane) did not show cytotoxicity against mouse cell fibroblasts, nZnO efficiently inhibited the growth of *Staphylococcus aureus* and *Escherichia coli* bacteria *in vitro* using flask shaking method and had effective antibacterial activity against gram positive and gram negative bacteria (23).

Chitosan as a gelling fiber has an impact on the clinical outcome of chronic wounds as indicated by a reduction in wound size, management of moderate to high exudate and reduced odor and an increase in healthy granulation of previously bleeding brittle tissue (5).

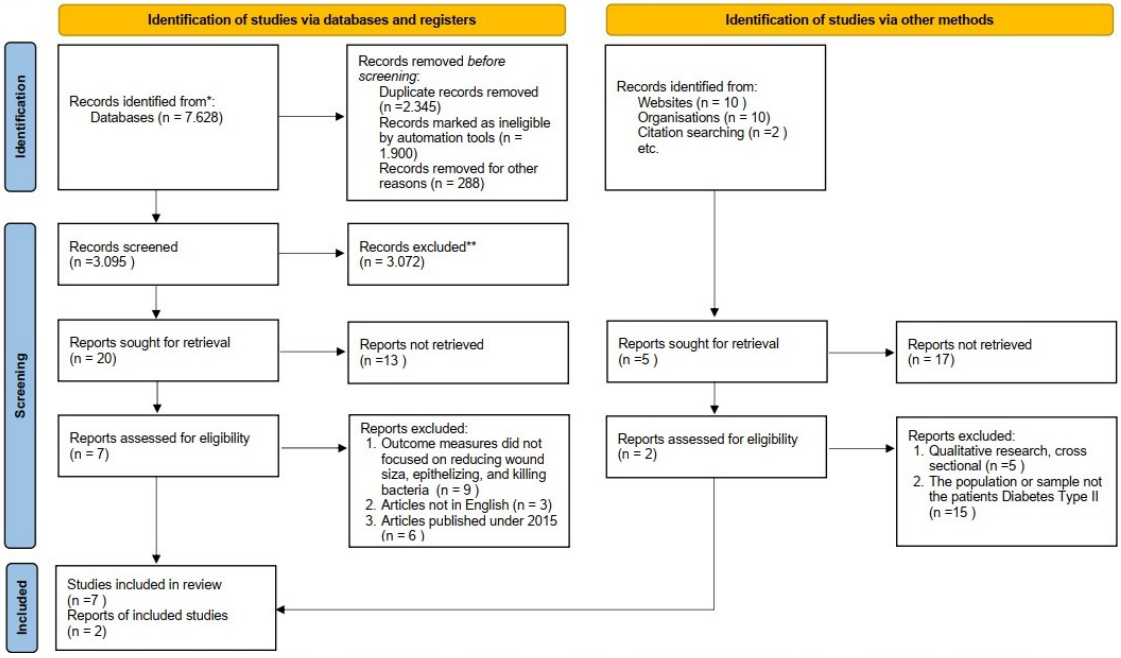


**Figure 1: Flow diagram of the systematic review process following PRISMA**

**Table II: Article Summary characteristic zinc chitosan and silver dressing**

| No | Author, Year, Journal, Country | Title Article | Aim & Total Respondent | Study Design | Intervention | *Validity & Realibility Instrument* | Statistic Test | Key Finding | Quality Appraisal | Ethics Approval | Limitation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Elgayyar, et al, 2019 Clinical Dermatology Review. Egypt | Evaluation of Chitosan Impregnated with Silver Nanoparticles in the Treatment of Chronic Venous Leg Ulcer: An Open-Label Controlled Study | Aim:<br>- Evaluating the effectiveness of chitosan, chitosan with silver nanoparticles (AgNPs) compared with compression dressings in the treatment of chronic venous leg ulcers (CVLU).<br>- Total respondent:<br>38 patients with CVLU of different sizes and durations with good general medical condition | Open-Label Controlled Study | - Compression bandage dressing impregnated with chitosan plus AgNPs, chitosan, and compression bandage dressing without chitosan or AgNPs.<br>- The dressing was applied twice/ weekly till either complete healing of the ulcer or for a maximum of 3months' duration<br>- Intervention group A: n=12<br>compression bandage dressing impregnated with chitosan plus AgNPs as gel was applied after ulcer clean from exudates, pus, and debris with normal saline.<br>Intervention group B: n=11<br>compression bandage dressing containing chitosan gel only after ulcer clean from exudates, pus, and debris with normal saline.<br>- Control group C: n=15<br>compression bandage dressing without chitosan or AgNPs after ulcer clean from exudates, pus, and debris with normal saline. | - The leg ulcer was measured by the modified Leg Ulcer Measurement Tool<br><br>- Color duplex ultrasound was done to evaluate vein anatomy and for assessing both reflux and obstruction within the deep, superficial or perforating veins, from the inferior vena cava to the calf veins | Chi square test and Mann–Whitney test. | chitosan, nanoparticles, silver, venous ulcer | Reasonable | Not mentioned | Needs more studies epidemiological characteristics of the patients, local examination, and bacterial culture in the studied groups |
| 2 | Mason and Clarke, 2015, British Journal of Nursing. England | A multicentred cohort evaluation of a chitosan gelling fibre dressing | Aim:<br>- To examine whether the new fibre dressing improved healing outcomes for patients with chronic non-healing wounds of 6 weeks or more observations were made regarding tissue type, fluid handling, haemostasis in bleeding friable wounds and increased granulation.<br>- Total Respondents:<br>18 patients with a history of chronic nonhealing wounds of 6 weeks or more | Case study | Promote epithelisation<br>Granulation<br>Remove slough<br>Reduce bioburden<br>Reduce malodour<br>Wound maturation<br>Manage exudate<br>Manage pain<br>Palliative care<br>Extend wear times<br><br>Eighteen patients were observed up to 4 weeks, or when the wound healed.<br><br>Wounds were assessed at each dressing change | The instrument used a questionnaire provided by the Aspen clinical team and local representatives | key indicators of chronic | Chitosan gelling fibre dressing, chronic wound care | Reasonable | Not mentioned | Several comorbidities and risk factors can cause delayed wound healing uestionnaire regarding pain and palliative care are ambiguous |
| 3 | Sutto, et al., 2018, Diabetes & Vascular Disease Research. Mexico | Efficacy and safety of the combination of isosorbide dinitrate spray and chitosan gel for the treatment of diabetic foot ulcers: A double-blind, randomized, clinical trial | Aim:<br>- To evaluate whether a combination of isosorbide dinitrate spray and chitosan gel (10%) topically applied can have additive benefits for management of diabetic foot ulcers.<br>- Total Respondent:<br>68 patients with DFU, Wagner grades I and II, Ankle–brachial index >0.8 and no prior treatments for foot ulcers were included | RCT | The combination of ISDN and chitosan increased the number of patients who reach complete ulcer closure compared with placebo:<br>Group 1 (n=17): treated with chitosan gel<br>Group 2 (n=17): isosorbide dinitrate spray<br>Group 3 (n=17): combination of isosorbide dinitrate spray and chitosan gel<br>Group 4 (n=17): placebo | the protocol was approved by the local bioethics committee of the Health Sciences University Center of the University of Guadalajara (number 030-2010) and published under clinical trial (NCT02789033) | The Shapiro–Wilk test was used to evaluate normal distribution Fisher's exact test<br><br>Cohen's d test | Diabetic foot ulcers; diabetic complications; isosorbide dinitrate spray; chitosan | Reasonable | Not mentioned | The difficulty in estimating the impact of the intervention over other factors that influence the healing process and co-exist in all patients, such as the metabolic control of the patients, the time of evolution of the ulcer, the presence of infection–contamination, neuropathyand peripheral vascular disease, all of which were taken into consideration to assure the homogeneity of the groups Sample was small to make definitive statements |

**Table II: Article Summary characteristic zinc chitosan and silver dressing**

| No | Author, Year, Journal, Country | Title Article | Aim & Total Respondent | Study Design | Intervention | *Validity & Realibility Instrument* | Statistic Test | Key Finding | Quality Appraisal | Ethics Approval | Limitation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | Luo, et al., 2020, International Journal of Nano-medicine. China | In situ Fabrication of Nano ZnO/ BCM Biocom-posite Based on MA Modified Bacterial Cellulose Membrane for Antibacterial and Wound Healing | Aim:<br>- To fabricate Nano ZnO/BCM with stable combination, select Nano ZnO/BCM with optimal Nano ZnO content which possesses antibacterial activity, homogenous distribution and has no cytotoxicity, and evaluate the possibility of the practical application of wound dressings to promote infected wound healing.<br>- Total Respondents: The mouse fibroblast cell L929 was purchased from the Type Culture Collection of the Chinese Academy of Sciences, Shanghai, China The New Zealand White rabbits and BALB/c mice were purchased from the Experimental Animal Department of the Third Military Medical University | In vivo, In vitro | The selected 5wt. % nZnO/BCM with well stability achieved network structure with high porosity, good physical properties, appropriate water vapor permeability, nontoxicity, antibacterial activity and good biocompatibility, and main-tain a nonseptic and normal wound microenvironment for tissue regeneration, leading to rapid re-epithelialization and wound closure, while causing no measurable damage to normal tissues | The Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Pub. No. 85-23, revised 1996) The mechanical properties of the BCM and the Nano ZnO/ BCM were measured by tensile testing | The antibacterial activity of the 5wt. % nZnO/ BCM against S. aureus and E. coli in vitro using shaking flask method To evaluate the actual bactericidal effect of nZnO/ BCM in vivo, wound bacteria were isolated and quantified using a method of biopsy homogenate | bacterial cellulose, nano-zinc oxide, in situ synthesis, antibac-terial, non-toxic-ity, wound dressing | Reason-able | All the animal experi-mental procedures had obtained the approval from the Animal Experiment Ethics Committee of the Third Military Medical University (Animal Ethical Statement). | Not carried out on experimental animals |
| 5 | Probst and Saini, 2019, JOURNAL OF WOUND CARE Zurich | Comparison of sterile polyacrylate wound dressing with activated carbon cloth and a standard non-adhe-sive hydrocellular foam dressing with silver: a ran-domised controlled trial protocol | Aim:<br>- To determine whether there is a difference in wound size reduction between wounds dressed with either a sterile poly-acrylate wound dressing with activated carbon cloth or a hydrocellular foam dressing with silver<br><br>- Total Respondents: 248 participants with a hard-to-heal wound in one wound care outpatient clinic | RCT | - Group 1 (sterile polyacrylate wound pad with activated carbon cloth dressing): visits to the outpatient wound care centre as directed by a physician. Wound care performed by the wound expert using cellulose and distinct layers of sodium-polyacrylate.<br><br>- Group 2 (hydrocellular foam dressing with silver): visits to the outpatient wound care centre as directed by a physician. Wound care performed by the wound expert using a standard foam dressing with silver. | Wound size images using advanced visual and infrared imaging device (3D wound im-aging device 13). This technology provides accurate and repeat-able measurements (length, width, depth, volume, perimeter and area), and allows, in addition, the visual-isation of metabolic/ temperature changes Evaluation of odour by patient and health professional using a VAS from 0 to 100 Patient Needs Questionnaire (PNQ) and Patient Benefit Questionnaire (PBQ), The Cronbach's Alpha for the French version is 0.74 for the PNQ scale and 0.85 for the PBQ scale. | a parametric test (t-test) or a non-para-metric test (Mann-Whitney U test) | benefit of treatment ; chronic wound; health-care ex-penditure; quality of life; wound dressing | Reason-able | Mentioned | Did not mention what are the factors that maked delay wound healing and the number of respondents in each group |





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**Table II: Article Summary characteristic zinc chitosan and silver dressing**

| No | Author, Year, Journal, Country | Title Article | Aim & Total Respondent | Study Design | Intervention | *Validity & Realibility Instrument* | Statistic Test | Key Finding | Quality Appraisal | Ethics Approval | Limitation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Stokes, Metcalf & Bowler, 2016, British Journal of Nursing. England | Management of diabetic foot ulcers: evaluation of case studies | Aim:<br>- Describes the use of a dressing designed to manage exudate, infection and biofilm (AQUACEL® Ag+ dressing (AQAg+)) on recalcitrant diabetic foot ulcers.<br><br>- Total respondent:<br>4 patients with slow-healing, static, or deteriorating DFUs | Case study | Knowledge in choosing the right dressing supports timely wound healing as well as overcoming biofilms can prevent infection, reduce length of stay and amputation<br>Using AQAg +, two from four cases experienced a complete cure and the two case latter experienced an important increase in recovery | A standard evaluation form was used for each patient to capture basic demographic information, as well as details of relevant medical history, prior treatments, and information relating to their DFU<br>before, during and after the evaluation | Previous research by Harding et al (2015) was followed by 42 patients in non-comparative clinical study in chronic venous leg ulcers | Biofilm; Diabetic foot; Exudate; Infection; Foot ulcer; Wound healing | Reasonable | Mentioned | There were no strict inclusion or exclusion criteria patients with DFUs and no culture test confirmed the presence of any specific bacterial infection |
| 7 | Tarusha, et al., 2018, Engineering and nano-engineering approaches for medical devices Italy | Alginate membranes loaded with hyaluronic acid and silver nanoparticles to foster tissue healing and to control bacterial contamination of non-healing wounds | Aim:<br>- A novel wound-dressing material based on a blended matrix of the polysaccharides alginate, hyaluronic acid and Chitlac-silver nanoparticles is here proposed and its application for wound healing is examined<br><br>- Total Respondent: | Biological in vitro studies | - biocompatible and biomaterials with a wide spectrum of antimicrobial efficacy and with the<br>capability to prevent biofilm formation, while at the same<br>time stimulating wound closure.<br><br>- A wound dressing material based on alginate, hyaluronan and Chitlac-nAg was successfully designed and<br>manufactured in the form of a pliable membrane by using a<br>technical procedure that could be easily scaled-up.<br>The membrane was shown to support in vitro the healing<br>process and to be effective against both planktonic bacteria<br>and bacterial biofilms. | Antimicrobial tests: Staphylococcus aureus (ATCC® 25923™), Staphylococcus epidermidis (ATCC® 12228™) and Pseudomonas aeruginosa (ATCC® 27853™)<br>Scratch wound healing assay | Silver release study: The amount of silver released from the membranes was quantified by Electro-Thermal Atomic Absorption Spectrometry (ETAAS)<br><br>Antibacterial activity against planktonic bacteria and mature biofilms by incubating the bacterial suspension with the membranes for 24 h. The Colony Forming Units per milliliter (Log CFU mL−1 ) calculated for each sample after 24 h are reported | Not mentioned | Reasonable | Not mentioned | Not carried out on experimental animals |

The use of a foam hydrocellular dressing with silver and a polyacrylate dressing with activated carbon resulted in a reduction in wound size, but was also effective in dealing with excessive exudate, foul odor, pain and maceration caused by wound infection with a frequency of dressing changes for 12 weeks and with additional secondary dressing (24).

The use of AQAg+ (AQUACEL ® Ag +) in four cases showed significant increase in healing in cases of DFU (Diabetic Foot Ulcer), namely two cases experienced complete healing and the remaining two showed significant increase in healing. AQAg+ is not only effective in the treatment of wound exudates, but also because it forms a gel, maintains moisture in the wound area, helps autolytic debridement and combines antimicrobial silver ion and anti-biofilm (25).

The combination of ISDN (Isosorbide dinitrate) and chitosan resulted in total wound closure in increased number of patients, but the sample size was small to make a definitive statement. An increase in angiogenesis as a growth factor and cytokines indicates wound healing (26).

Bandages made from alginate, hyaluronan and Chitlac (lactose-modified chitosan, CAS number 85941-43- 1) -nAg in the form of membranes are effective in vitro against both planktonic bacteria and bacterial biofilms. This membrane prevents the formation of bacterial colonization and treats infected wounds. Chitlac-AgNPs (silver nanoparticles) have been shown in vitro to inhibit the proteolytic activity of MMP (Matrix metalloproteinases) which can cause wounds to experience delayed healing (27). DM patients are must be alert of their disease and must have desirable knowledge to overcome poor practice of foot care. Strategies to expand network of diabetes awareness with implementation of primary prevention programs regarding foot care required (28,29).

## CONCLUSION

Based on the above research on analysis using a systematic review method, it can be concluded that the factors that greatly affect wound healing are Chitosan-based materials and silver dressings that aim to kill bacteria in diabetic ulcers so that treatment time can be shorter. Bacteria as bioburden can be destroyed by zinc chitosan cream and silver dressing. Both wound dressings function as antimicrobials agents, so researchers feel it is necessary to conduct further research to compare the effectiveness of the two materials in a semi-experimental way to detect the effect on healing process of diabetic ulcers in patients with type II Diabetes Mellitus. The present study can serve as a reference for improving nursing services towards the benefits of modern dressings on diabetic ulcer healing.

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