

# Bioactive Glass Based Materials with Possible Application in Diabetic Wound Healing: A Systematic Review

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**Disclosures:** Marian Vargas Guerrero (Bonalive Biomaterials), Floor M.A Aendeker (N), Jacobus J.C. Arts (Bonalive Biomaterials), Candice de Boer (N), Jan Geurts (Bonalive Biomaterials).

**INTRODUCTION:** Diabetes affected 537 million adults in 2021; costing a total of USD 966 billion dollars [1]. Most common complications associated with diabetes correspond to the development of diabetic foot ulcers (DFU), which if left untreated can lead to osteomyelitis or even amputation [2]. DFU ulcers affect around 15% of diabetic patients; these ulcers have impaired healing due to neuropathy, arterial disease, infection, aberrant extracellular matrix (ECM) degradation, among other factors. To find solutions to aid with wound healing it is important to understand how the healing process works. It consists of four overlapping stages, being hemostasis, inflammation, proliferation and remodeling (Figure 1). This systematic review focuses on assessment of bioactive glass (BG) based materials to aid diabetic wound healing and intends to contribute to the advancement of therapeutic strategies development to treat diabetic wounds.

**METHODS:** The PRISMA statement 2020 for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions has been followed for this systematic review [3]. The systematic review protocol was submitted to the Open Science Framework (OSF) <https://osf.io/bfhpm>.

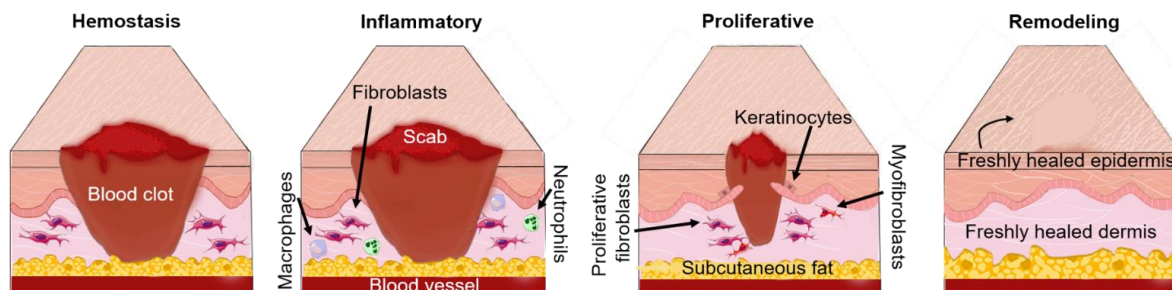
**RESULTS SECTION:** A total of 39 articles without duplicates were screened, from which 14 were excluded based on title and abstract, of the remaining 25 articles, 6 were excluded based on full text screening, and in the end 19 articles were included in this systematic review. The materials from the studies were classified in 3 groups: hydrogels (7), electrospun micro/nano fiber/scaffolds (7) and miscellaneous (5) which included ointments, multilayer composites and extracts. Data on material synthesis, cytocompatibility, antimicrobial properties, angiogenesis promotion *in-vitro* and *in-vivo* and wound healing *in-vivo* was extracted. 15 out of the 19 articles studied cytocompatibility and showed that their materials were cytocompatible. Angiogenesis promotion *in-vitro* was studied by 10 out of the 19 articles, they showed either by tube formation assay or by the upregulation of angiogenic markers such as VEGF that their material could increase angiogenesis in comparison to the control group. The antimicrobial properties of the material were the least studied as only 5 out of the 19 articles investigated them, showing in all cases a decrease in bacterial colonies in comparison to the control. Finally, all studies used a diabetic animal model (mouse, rat or rabbit) to investigate the effect of their material in diabetic wound healing, showing that their materials helped achieve a higher wound closure percentage in a shorter time period in comparison to the controls.

**DISCUSSION:** The BG based materials discussed in this systematic review show promising results in accelerating diabetic wound healing, as seen in their respective *in-vivo* diabetic animal studies. It can be concluded that the addition of BG is extremely valuable with regards to the wound healing rate and wound healing quality, since BG activates fibroblasts, enhances M1-to-M2 phenotype polarization in macrophages promoting the transition to the proliferative stage of wound healing, induces angiogenesis, initiates the formation of granulation tissue and re-epithelialization of the wound. In addition, a higher density, deposition, and better organization of collagen type III is seen in the wounds treated with the materials containing BG. The *in-vitro* studies performed by most of the authors were not performed in a high glucose environment, not evaluating the effect of diabetes *in-vitro*, we recommend future studies simulate the diabetic wound environment in their *in-vitro* work. There was a lack of antimicrobial studies performed to the materials, as diabetic wounds are susceptible to infection and bioactive glass has known antimicrobial properties, we consider this an important factor to study. The cost-effectiveness of the newly proposed materials should also be considered to determine if the material is a solution that could be used in clinical practice.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Accelerating diabetic wound healing is crucial as it can prevent the development of a chronic ulcer, osteomyelitis or even an amputation. Therefore, it is relevant to be aware of the different material solutions being developed to aid diabetic wound healing and determine which ones have potential to be implemented in the clinic.

## REFERENCES:

1. International Diabetes Federation, *IDF Diabetes Atlas*. 10 th ed. 2021: International Diabetes Federation.
2. Gupta, A.K., *Understanding the Risk Factors for Developing Diabetic Foot Osteomyelitis*. J Bone Res, 2023. **11**: p. 210.
3. Page, M., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*. BMJ, 2021. **71**.



**Figure 1. Wound healing stages** Processes that occur during the different wound healing stages. **i. Hemostasis:** Occurs immediately after tissue damage to stop bleeding by platelet aggregation and the coagulation cascade. **ii. Inflammation:** Removal of the bacteria and dead cells in wound bed by inflammatory cells (neutrophils and macrophages). Triggers the proliferation stage. **iii. Proliferation:** Proliferation and migration of fibroblasts, keratinocytes and endothelial cells. Re-epithelialization, angiogenesis, and granulation tissue formation. **iv. Remodeling:** Reorganization of ECM, collagen type III is replaced by collagen type I, it can last one year or more.