Novel Bioengineered Collagen with Manuka Honey and Hydroxyapatite Sheet for the Treatment of Lower Extremity Chronic Wounds in an Urban Hospital Wound Care Setting

Isaac Rodríguez, PhD[1]; Alejandra Alvarez, PMP, CPXP[2]; Cara Massey, FNP-C[3]; LaDawn Miller, PA-C[3]; Rene Rannou, CHT, DMT[3]; Martin Croce, MD[4]; and Tony Alleman, MD, MPH[3]

Acknowledgments: The authors thank Tracy LeGros, MD, PhD, for her contributions to this study.

Affiliations: [1]SweetBio, Inc, Memphis, TN; [2]Regional One Health, Center for Innovation, Memphis, TN; [3]Regional One Health Wound Care Center, Memphis, TN; [4]Regional One Health, Memphis, TN

Disclosure: I.R. is an executive of SweetBio, Inc. A.A., C.M., L.M., R.R., M.C., and T.A. are employees of Regional One institutions. Regional One Health has a financial interest in SweetBio, Inc, through services, not cash. SweetBio, Inc, provided the product for this study at no charge.

Correspondence: Isaac Anthony Rodríguez, PhD, SweetBio, Inc, 460 S. Highland St. Suite 200, Memphis, TN 38111; isaac@sweetbio.com

Recommended Citation: Rodríguez I, Alvarez A, Massey C, et al. Novel bioengineered collagen with Manuka honey and hydroxyapatite sheet for the treatment of lower extremity chronic wounds in an urban hospital wound care setting. *Wounds*. 2023;35(1):E35-E38. doi:10.25270/wnds/22034

ABSTRACT

Introduction. A novel BCMH sheet has been shown to achieve improved wound closure rates in chronic and acute wounds when compared with SOC. **Objective.** This retrospective evaluation assessed chronic wound closure rates with SOC or treatment with the BCMH sheet in an urban hospital wound clinic. **Methods.** Forty-seven chronic wounds were treated with either SOC or the BCMH sheet. The primary endpoint was time to closure. For wounds that did not close, investigations were conducted to determine the reason. **Results.** Twenty wounds were treated with SOC, which varied in usage of multiple products and/or therapies, and 27 wounds were treated with the BCMH sheet. The average initial wound size was not statistically different between the groups. In both groups, most wounds that were treated did not close. For wounds that did close, the average time to closure was two times faster in the BCMH group compared with the SOC group (7.4 weeks and 14.8 weeks, respectively; $P < .05$). **Conclusions.** This retrospective evaluation showed average time to wound closure to be significantly faster with BCMH compared with SOC in patients who maintained adherence with regular visits.

Keywords: diabetic foot ulcer, lower extremity, wound healing, collagen, Manuka honey, health disparities, hydroxyapatite

Regardless of anatomic location, wounds are complex and require a multifaceted approach for healing.[1] However, current products have restricted ability for healing complex wounds. Manuka honey is one of few scientifically validated materials capable of this advanced approach because it is antibacterial, deregulates harmful MMPs, and upregulates pro-regenerative growth factors.[2-4] It is unusable for advanced treatments in its messy, short-term, topical form, however. Collagen and its derivatives are also attractive materials in wound care because they can buffer harmful high levels of MMPs by acting as a sacrificial substrate.[5,6] However, additional materials and/or compounds (eg, silver) must be incorporated to pursue a more comprehensive approach for healing.

APIS (SweetBio, Inc) is a novel, US Food and Drug Administration–cleared and CMS–covered wound care product (FDA 510[k] 182725 and HCPCS Code A6021 Collagen Dressing) that uniquely synthesizes a collagen derivative (gelatin), Manuka honey, and hydroxyapatite (a naturally occurring inorganic mineral) into a solid sheet for the management of wounds (**Figure 1**). In earlier clinical evaluations, use of this absorbable BCMH sheet has been shown to result in closure of chronic and acute wounds in an average of 4 to 6 weeks.[7,8] Published in vitro data demonstrated that the BCMH sheet comprehensively reduced bacterial load, decreased MMP-9, and triggered the release of

Abbreviations: BCMH, bioengineered collagen with Manuka honey and hydroxyapatite; CMS, Centers for Medicare & Medicaid Services; DFU, diabetic foot ulcer; MMP, matrix metalloproteinase; SOC, standard of care.

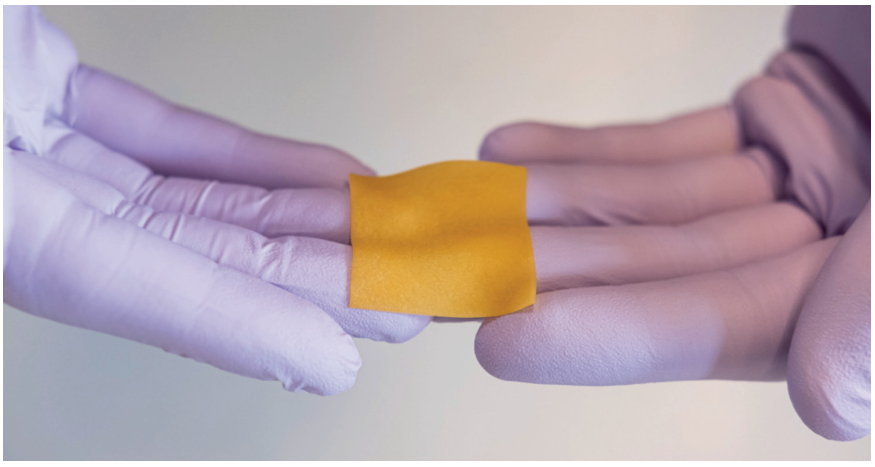

Figure 1. A sheet of the hydrated bioengineered collagen with Manuka honey and hydroxyapatite used in this study.

Table 1. Patient Demographics

VARIABLE	BCMH	SOC
No. of patients	23	20
Age (y), mean ± SD	62 ± 6	57 ± 4
Sex (n [%])		
Male	15 (65)	13 (65)
Female	8 (35)	7 (35)
Ethnicity (n [%])		
African American	11 (48)	16 (80)
White	10 (43)	2 (10)
Hispanic	2 (9)	2 (10)

Abbreviations: BCMH, bioengineered collagen with Manuka honey and hydroxyapatite; SD, standard deviation; SOC, standard of care; y, year(s).

Table 2. Wound-related Data

VARIABLE	BCMH	SOC
No. of wounds	27	20
Wound size (cm^2), mean ± SD	1.6 ± 0.8	2.1 ± 0.8
Wounds closed (n [%])	7 (26)	8 (40)
Time to closure (wk), mean ± SD[a]	7.4 ± 5.8	14.8 ± 5.6
Wounds not closed (n [%])	20 (74)	12 (60)

Abbreviations: BCMH, bioengineered collagen with Manuka honey and hydroxyapatite; SD, standard deviation; SOC, standard of care; wk, week(s).
[a]Statistically significant difference ($P < .05$).

growth factors, all of which contribute to instill balance to the microenvironment and progress wounds towards healing.[9,10]

The purpose of this IRB-approved retrospective clinical evaluation (No. 21-07962-XM) was to assess chronic wound closure rates with the BCMH sheet versus SOC in 43 patients treated in a level I urban trauma center wound care department (Regional One Health) in Memphis, Tennessee, where over 20% of patients are uninsured and do not receive the consistent comprehensive care they need outside of the center. A secondary area of interest was patient adherence to help provide insights into external factors that affect wound healing.

MATERIALS AND METHODS

Included patients were age 18 years and older, were ambulatory, and had adequate circulation, type 1 or 2 diabetes, and a wound surface area (length × width) less than or equal to 9 cm^2. Additional inclusion criteria were nonhealing wounds, no clinical signs of infection, and, for DFUs, Wagner grade 1 or 2. For all patients, wounds were cleaned, debrided, measured, and photographed prior to any product application. If any product was used, it was covered with a secondary dressing and secured in place via compression wrapping. Patients were instructed to offload and not change dressings until the next visit in 1 week. Patient demographics; wound type, duration, and size; number of visits; number of products used; time to closure (complete reepithelialization); and reason for stopping treatment (if the wound did not close) were documented. A 1-way analysis of variance statistical analysis with $P < .05$ considered to be significant was performed on wound size and time to closure for wounds treated with BCMH or SOC.

RESULTS

A total of 47 wounds from 43 patients were evaluated. Patient demographics are shown in **Table 1**, and patient wound data are shown in **Table 2**. Thirty-eight wounds (80%) were DFUs, with the majority located on the plantar surface or the toe. Other wound types included pressure ulcers and venous leg ulcers. Twenty wounds were treated with SOC, which included various products and/or therapies, such as silver foams; cadexomer iodine; silver-coated, high-density polyethylene meshes; collagen sheets;

mafenide acetate cream; silver nitrate; and hyperbaric oxygen. Twenty-seven wounds were treated with the BCMH sheet, with reapplications recommended per instructions for use.

There was no statistically significant difference in average initial wound size between the SOC group (2.1 cm^2) and the BCMH group (1.6 cm^2). The percentage of wounds closed was slightly higher in the SOC group than in the BCMH group (40% and 26%, respectively). However, the average time to wound closure was 2× faster in the BCMH group compared with the SOC group (7.4 weeks and 14.8 weeks, respectively; $P < .05$). Photographic examples of wound closure in each group are shown in **Figure 2**.

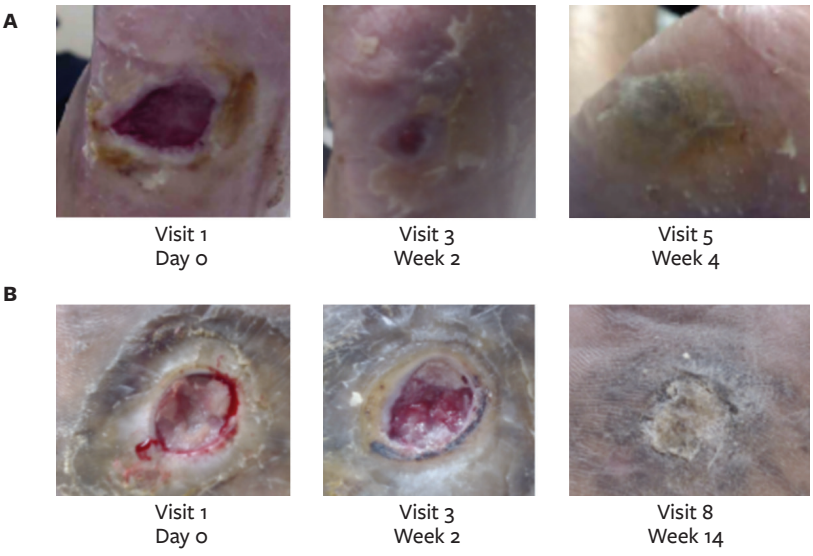

Figure 2. Progression of plantar diabetic foot ulcers in 2 different patients, treated with either (A) BCMH or (B) SOC. (A) The wound treated with BCMH measured 2 cm^2 at visit 1 (day 0) and 0.54 cm^2 at visit 3 (week 2). Wound closure was achieved by visit 5 (week 4). (B) The wound treated with SOC measured 2.72 cm^2 at visit 1 (day 0) and 1.95 cm^2 at visit 3 (week 2). Wound closure was achieved by visit 8 (week 14).
Abbreviations: BCMH, bioengineered collagen with Manuka honey and hydroxyapatite; SOC, standard of care.

DISCUSSION

In both the BCMH and SOC groups, most of the treated wounds did not close. This is consistent with a literature review published in 2018, which reported that real-world data from the US Wound Registry and randomized controlled trials as well as publicly reported wound outcomes provide convincing evidence that wound healing is not achieved in most patients (55%–70%), which is considerably different from a publicly reported mean healing rate of 92%.[11] The authors of that 2018 review further stated that it is likely that in a real-world setting with complicated patients, such as in an urban hospital wound care center, healing rates over 40% are not achievable.[11] To further understand this phenomenon, the authors of the present study investigated the reasons wounds did not close. The top reasons for lack of wound closure were nonadherence (ie, missing appointments, not offloading, dietary indiscretion; 14 patients), comorbidities (6 patients), reclassification (wound initially treated as Wagner grade 2 but reclassified to Wagner grade 3 and then treated outside of this study; 5 patients), and change in treatment facility location (3 patients).

A notable case to highlight is a patient who had a DFU of more than 6 months' duration on each foot with no progress using SOC. This patient was not strictly compliant with offloading; the patient enjoyed going to the store and playing with their grandchildren. In this scenario, the patient served as their own control. The BCMH sheet was used to treat the left foot, and SOC was used to treat the right foot. Within 6 weeks, the wound treated with the BCMH sheet was closed, whereas the wound treated with SOC remained open. At that time, the BCMH sheet was used to treat the wound on the right foot; after 2 weeks, that wound closed. This case produced results similar to the overall findings in that treatment with the BCMH sheet facilitated faster wound closure.

LIMITATIONS

As with any retrospective study, there are limitations to controls. However, the study design and number of patients provide sufficient data for analysis and sound interpretations. A future study, such as a randomized controlled trial, would be a valuable next step to further investigate these results.

CONCLUSIONS

Previously published clinical evaluations of the BCMH sheet have shown average time to wound closure of 4 to 6 weeks for chronic and acute wounds.[7,8] This retrospective clinical evaluation involved use of the BCMH sheet in an urban hospital wound care center where patient adherence and comprehensive care are significant challenges. The results and observations from this evaluation support the use of the BCMH sheet to improve average time to closure compared with SOC from 14.8 weeks (SOC) to 7.4 weeks (BCMH) in patients who maintained adherence with regular visits.

REFERENCES

1. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)*. 2015;4(9):560-582. doi:10.1089/wound.2015.0635
2. Sell SA, Wolfe PS, Spence AJ, et al. A preliminary study on the potential of manuka honey and platelet-rich plasma in wound healing. *Int J Biomater*. 2012;2012:313781. doi:10.1155/2012/313781
3. Afrin S, Giampieri F, Forbes-Hernández TY, et al. Manuka honey synergistically enhances the chemopreventive effect of 5-fluorouracil on human colon cancer cells by inducing oxidative stress and apoptosis, altering metabolic phenotypes and suppressing metastasis ability.

Free Radic Biol Med. 2018;126:41-54. doi:10.1016/j.freeradbiomed.2018.07.014
4. Bernstein RC. The scientific evidence validating the use of honey as a medicinal agent. *The Science Journal of the Lander College of Arts and Sciences*. 2013;6(2).
5. Brett D. A review of collagen and collagen-based wound dressings. *Wounds*. 2008;20(12):347-356.
6. Bohn G, Liden B, Schultz G, Yang Q, Gibson DJ. Ovine-based collagen matrix dressing: next-generation collagen dressing for wound care. *Adv Wound Care (New Rochelle)*. 2016;5(1):1-10. doi:10.1089/wound.2015.0660
7. Rodriguez IA, Strombergsson A, Weinstein R, et al. Preliminary clinical evaluation using a novel bioengineered wound product to treat lower extremity ulcers [published online ahead of print, 2020 Oct 30]. *Int J Low Extrem Wounds*. 2020;1534734620968378. doi:10.1177/1534734620968378
8. McMurray SL, Wallace MM, Stebbins WG, Clayton AS. Use of a novel biomaterial to enhance secondary intention healing. *Dermatol Surg*. 2021;47(6):843-844. doi:10.1097/DSS.0000000000002725
9. Rodriguez I, Conti T, Bionda N. Microenvironment influence of a novel bioengineered wound product, APIS®: a preliminary in vitro analysis of inflammatory marker and growth factor secretion. *Int J Biomater*. 2021;2021:6612870. doi:10.1155/2021/6612870
10. Williams M, Rodriguez I, Strombergsson A, Fabbri S, Westgate S. A novel bioengineered wound product with in vitro capabilities to reduce bacteria. *Biomed Transl Sci*. 2021;1(1):1-3.
11. Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. *Adv Wound Care (New Rochelle)*. 2018;7(3):77-94. doi:10.1089/wound.2017.0743