ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

MULTI MODAL APPROACH TOWARDS MANAGEMENT OF DIABTEIC FOOT ULCERS: A SYSTEMATIC REVIEW

DR. BRIJENDRA NIGAM, DR. MANISHA NIGAM, DR. APOORVA SRIVASTAVA, DR.PRADEEP TANDON

RAMA MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, RAMA UNIVERSITY, MANDHANA- KANPUR RAMA MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, RAMA UNIVERSITY, MANDHANA- KANPUR, RAMA INSTITUTE OF PARAMEDICAL SCIENCES, RAMA UNIVERSITY, RAMA UNIVERSITY, MANDHANA- KANPUR RAMA MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, RAMA UNIVERSITY, MANDHANA- KANPUR (Corresponding Author) Dr. Manisha Nigam, E-mail:drmanishanigam@gmail.com

ABSTRACT:

Diabetes is a major concern as it has serious consequences and tends to widen its realm with each passing year. People suffering from diabetes suffer from various commodities which worsens their condition and most common of these is the development of Diabetic foot ulcers. There have been many strategies in respective fields in order to combat these ulcers but there is still need of a definite Multi-modal approach to achieve maximum benefit for the patients. This is a systematic review which aims to explore the various treatment strategies available for the treatment of Diabetic foot ulcers from the perspective of a rehabilitation team which will combine the available and promising interventions prevalent for the treatment purpose. A total of 15 articles were selected for review purpose on the basis of their quality and the results they showed from different approaches. The treatment strategies could be provided by various professionals like General Surgeons, General Physician, Diabetologists, Physiotherapists, Nursing care, Nutritionists, Care givers, etc. However, the newer modern medicine has a tremendous impact on the overall quality of life of patients with such disorders and have promising effects on foot ulcers especially which is one of the leading causes of deaths of individuals suffering from diabetes. Promotion of rehabilitative measures for such patients which will use expertise of various medical professionals which develop strategic decisions for more such diseases in future.

KEYWORDS: Diabetes Mellitus, Diabetic Foot Ulcer, Surgery, Medicine, Quality of life

INTRODUCTION:

Diabetes is said to be one of the most expensive lifestyle diseases in the world which is expanding its horizon not only in terms of the ailments or comorbidities associated with the disease but in terms of the total healthcare expenditure on the treatment of these comorbidities. Development of ulcers or wounds may have varied physiological reasons but the most common cause behind its formation is the presence of diabetes in such individuals which makes it tougher for the patients to combat such proceedings. Not only the healthcare system of any country is facing problems, but this has created a sort of economical insufficiency in terms of expenses and healthcare services for the common individual to benefit from.² Most of the studies published earlier in this respect have calculated the total expenditure of burden of developing such a disease in an individual to be up to 10% of an annual expenditure on health an individual targets. These parameters were studied before the world hit the pandemic COVID-19, after this pandemic there must have been a drastic increase in the number of individuals suffering from such lifestyle diseases.³ Present case scenario of such problems requires time bound, specific, comprehensive and effective treatment strategies to meet the demands of the ever-growing healthcare sector in this respect.4

ISSN: 0975-3583. 0976-2833

VOL13, ISSUE 7, 2022

As a matter of concern, people suffering from diabetic foot or ulcers have numerous ailments incorporated within the disease that it becomes quite unmanageable to formulate a precise yet comprehensive treatment regime for such patients and to provide them with utmost precise combination of newer techniques and older treatment strategies.⁴ Authors who have worked on the treatment options available for Diabetic foot have studied various strategies which might benefit the patients in respect to their wound clearance, pain management and enhancement of their quality of life.¹ But there is still a lacuna in terms of a concise rehabilitation procedure or treatment strategy which will decrease the size of the ulcer, control the infection occurring from the ulcer and clearance of this ulcer from the site. There have been many strategies in respective fields in order to combat these ulcers but there is still need of a definite Multi-modal approach to achieve maximum benefit for the patients.

METHODOLOGY:

This is a systematic review which aims to explore the various treatment strategies available for the treatment of Diabetic foot ulcers from the perspective of a rehabilitation team which will combine the available and promising interventions prevalent for the treatment purpose. This review consists of articles searched form various databases such as PubMed, Scopus, Cochrane library and Google Scholar which yielded a number of articles. The search strategy opted for this review is depicted in **Table 1**. After thorough inspection and removal of duplication a total of 15 articles were selected for review purpose on the basis of their quality and the results they showed from different approaches. Articles were included which were published within a gap of 10 years, i.e., from 2013 up till July 2023, articles which were available in open access online and articles which had positive results after application of the strategy. Articles which were excluded included those that were case studies or case series, articles which were older than 2013, and articles which did not show any significant improvements in patients.

(Table 1): Search Strategy:

Terms	Search Strategy
Population	Patients with Diabetic Foot
Intervention	Surgical Interventions, Conventional Interventions and Ergonomical Interventions
Comparison	Comparison with any established strategy
Outcome	Clearance of Diabetic Foot Ulcers or reduction in their size

FINDINGS:

Treatment of Diabetic foot ulcer (DFU) requires an explorative yet concise and comprehensive treatment plan which will incorporate the expertise of various professionals in order to provide patients with optimal care and treatment. The treatment strategies could be provided by various professionals like General Surgeons, General Physician, Diabetologists, Physiotherapists, Nursing care, Nutritionists, Care givers, etc. Treatment strategy of Diabetic ulcers work on the principle of **TIME** which is duly explained as the treatment which incorporates collective efforts of professionals within a rehabilitation team set-up to provide:

ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

T- debridement or clearance of the affected **T** issue which will help clear the site of the wound or ulcer and make it free from pathogens

I – controlling the *I*nfection at the site of wound or ulcer

M- maintaining a balance between the Moisture of the skin tissue and surrounding tissues, and,

E- clearance of the Edge of the wound which will make it even for the area to heal appropriately.⁵

The various strategies which were found to be relevant and of high importance in the treatment of DFU are mentioned in **Figure 1**. Articles suggest that interventions for DFU must follow a rehabilitative theme which uses various healthcare professionals and to apply various useful and conjoint treatment strategies.

(Figure 1): Interventions available for DFUs



Treatment Strategies opted by General Surgeons/ General Physicians: As the first line of defence for the treatment of Diabetic Foot ulcers, there are numerous treatment strategies available which are promising and have shown tremendous results in the past years to clear and reduce the size of the ulcers. Some of these include:

a. **DRESSING AND DEBRIDEMENT**: Wound clearance and debridement is a necessary technique which not only clears the wound bed but makes it suitable for

ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

healing process to initiated by the body through various mechanisms. The cellular and molecular debris at the ulcer site is cleared through the process of debridement which involves surgical clearing of the site. Infiltration of the bacterial and fungal cells and micro-organisms into the site of the wound.⁶

- b. *OFF LOADING SURGICAL INTERVENTIONS*: Generally used for the patients with a wound grade of III and IV these are the surgical techniques which have shown quicker and better results in terms of clearing the site of ulcer from pathogens and marking a symmetry in the edges of the wound so that it becomes easier and quicker for the ulcers to heal. These off-loading procedures may involve a series or a combination of procedures which includes the sectioning of the lesser toes which involves resectioning and release of the flexor tendons especially done with patient having hammer toe and decompression of the hammer toe, resectioning or counter sectioning of the metatarsal heads or metatarsal offloading which involves release of Achilles tendon and reduction of the equines foot for correction of the foot deformities and ulcers, surgical interventions for the great toe and release of the hallux which involves a well-known surgical procedure termed as Keller's phenomena and various other structural deviations of the foot.
- c. APPLICATION OF DERMAGRAFT: Application of a skin graft or a part of skin over the site of ulcer or wound after its debridement is another promising treatment strategy to be used by General Surgeons in such patients.⁸ These grafts render medicinal and cellular infiltration at the site of ulcer which promotes healing and in turn rejuvenates the healing process and strengthen the clearance of the site from pathogens. Infiltrations using T-cells and other anti-inflammatory interleukins is an essential component of the grafting procedure. This graft could be an autogenic, allogenic or xenogeneic form of graft which can be utilised for various benefits such as protection of the site of ulcer, remodelling of the site and many a times these grafts are incorporated with medicines or extracellular components which makes the healing of the ulcer instigated and play a role in making the ulcer in contact with medicinal dosage for longer duration of period as compared to topical elements.⁹
- d. *NEGATIVE PRESSURE WOUND THERAPY*: This therapy involves surgically implementing a negative pressure with the help of Vacuum assisted instruments attached at the site of wound or ulcer so that the vacuum creates a negative pressure of about -125 mm of Hg continuously so that the area specified after debridement of the wound can be fixed and filled with internal tissue and haemopoietic cells. In this procedure after debridement of the site, a polyurethane foam piece is placed measuring around 400-600micron meter, connected to a VAC therapy unit administering a continuous and constant pressure for about 24 hours after which the piece is changed to another foam which will again exert the same amount of pressure. And finally, the size of the wound will be calculated 10
- e. **HYPERBARIC OXYGEN THERAPY**: Application of 100 percent oxygen to patients at the site of wound or ulcer two to three times as compared to the atmospheric sea level which instigates the normal physiological response of tissue healing and

ISSN: 0975-3583. 0976-2833

VOL13, ISSUE 7, 2022

innumerate several physiological mechanisms to happen at a faster speed than usual is termed as hyperbaric Oxygen therapy. This therapy introduced by Henshaw is a promising therapy for treatment of Diabetic Foot ulcers. This therapy works on the phenomena that increasing the pressure within the arteries and the veins causes this oxygen to render therapeutic benefits by increasing the blood flow to the region and enhancing the interleukins at the site. ¹¹

- f. SUSTAINED RELEASE NANO-SYSTEMS: Use of electronically spun biofilms that make the debrided or ulcer site in constant contact with a biofilm plating that introduces medicinal tea tree elements into the site of ulcer to make it free from pathogens and infections is termed as Sustained release nano-systems. It is newer technique and has promising effects in releasing antibacterial medicines to the site and making it free from any bacterial invasions and thus increasing the infection. 12
- g. **TOPICAL APPLICATION**: application of ointments at the site and around the surrounding structures is an older but promising treatment strategy that could benefit the patients as they have the ability to self-administer these drugs and make the site infection free and protected. The most commonly and prescribed among these is the Resina Draconis which is well established to have a very stable effect on the infection control and boundaries of the ulcer- 13

Treatment Strategies opted by Physiotherapists: From the perspectives of a physiotherapist there are some strategies which have gained importance in the past few years and have promising effects on ulcer size, pain due to ulcers and their clearance as well. These strategies include:

- a. *PHOTO-BIO-MODULATION*: Photo biomodulation refers to the usage of radiation therapy for the treatment of ulcers or wounds. This therapy involves administering light energy at a constant speed and frequency to generate heating effect within the tissues and cells surrounding the ulcers which it is free from pathogens, bacteria and infections and also helps in increasing the blood flow to the region which make its quicker for the wounds to heal. Use of radiation therapies such as Low-level LASER therapies, Ultraviolet radiations and Infrared radiations are being frequently used to alter the patho-physiology of the mechanisms undergoing at the site.
- b. TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION: Stimulations provided through TENS can also be beneficial in reducing the size of the ulcer and promoting sensory and motor growth of the neural endings at the site of ulcer which enhance the blood flow towards the site and make it easier for the interleukins and other cell mediators to reach the site of ulcers and promote healing. Application of TENS is usually delivered in the pattern of contralateral application of red and black electrodes. This phenomenon regulated the triggered procedures and then formulates the infiltration of the interleukins and antibodies towards the site by increasing blood flow to the region. ¹⁶

VOL13, ISSUE 7, 2022

ISSN: 0975-3583, 0976-2833

c. **SHOCK WAVE THERAPY**: Application of high energy based acoustic energy sources for administration into body through a beam of ray which produces anti-inflammatory effects at the site of application is termed as Shock wave therapy or Extra-corporeal shock wave therapy.¹⁷ In this therapy the beam is generated within the device and is transferred to site on human body by the help of transducer. It has promising effects in reducing the size and dys-symmetry of the ulcer or wound. ¹⁸

- d. *DRY NEEDLING:* This is a newer concept which involves invasion of thin therapeutic needles around the site of ulcer or wound which enhance the activity of cells surrounding the ulcers and increases blood flow to the area concerned. This increased blood flow rejuvenates the neural structures present at the site and thus aids in increasing the speed of healing. 19
- e. *TRANSFER TECHNIQUES*: Patients suffering from foot ulcers, usually have deprived weight acceptance and weight balance. Treating such patients with exercises that aim to establish a stable transference from one plinth to another or one chair to another will not only enhance their independency but will also tend to motivate mobility in such patients. ²⁰

Treatment Strategies opted by Nutritionists: Apart from these techniques, there are some nutritional deficient which enhance the delay in ulcer healing and provides inflammatory enhancement to the body. Delivering such patients with Vitamin C, Vitamin A, Vitamin D, zinc, arginine and glutamate has some promising effects on the process of healing.²¹ These minerals are said to enhance the speed of the tissue healing proliferate newer cells at the site of ulcers. Incorporating nutritional supplementations in diets of patients may benefit the additional support to medicines and exercise therapies. ²²

Treatment strategies opted by Nursing Care: Nursing care plays a keen role in managing the Diabetic foot ulcers in patients especially those are bed ridden and need assistance either partially or maximally. Application of positioning schedules adopted by nursing staff not only reduces the incidence of developing ulcers or wounds in such patients but also tends to restrict the wound or ulcer within its boundaries by removing all sort of extra pressure from the site of ulcers. ²³

Patient's Caregivers: It is very important to educate the caregivers of the patients about the possible comorbidities that may assist with the patients during the course of the disease and it is very important for the patients that they have a constant emotional and physiological support from their care givers as it gives the patients the strength to combat intensive treatment strategies.²⁴

DISCUSSION:

Diabetes is a leading cause of disability and impairments in the world. May it be a developing country or a developed one, this disease has spread its boundaries in various parts of the world because of its easily adjustable and non-seriousness of individuals towards their health.³ In leading countries there are still better resources and opportunities to combat such disease but in countries that are still developing it becomes difficult for the government and the patients to survive with this sort of disease.⁸ There are numerous comorbidities associated with diabetes which have more profound effect on human health than directly diabetes has,

ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

but still people tend to be very ignorant of the fact that any physiological abnormalities within level of glucose can cause a negative impact over the overall health of the individual ²⁴

Increasing comorbidity and increasing trend of patients with diabetes, has led to an unjustified burden over the healthcare delivery system which is making it even difficult for the healthcare professionals to render quality treatment and aids to every individual, especially in areas where there is scarcity of funds, medicine and resources. This has directly impacted the living standards of population leading to increase in causes of lifestyle modifications which again is responsible for developing diabetes in patients. There has been an almost 19-34% rise in the count of individuals worldwide who have developed diabetes. Most of them have one or another form of associated disorder related to diabetes which is itself worthy of taking interventions or medical advice. Not only the treatment strategy but application of several treatments becomes difficult once the patient is diagnosed with diabetes.

However, the newer modern medicine has a tremendous impact on the overall quality of life of patients with such disorders and have promising effects on foot ulcers especially which is one of the leading causes of deaths of individuals suffering from diabetes.²¹ Debridement and dressing strategies with the help of newer techniques have been proven to be very useful and of greater importance as it is now possible to debride and clear the site of infection or ulcer with application of topical medicine at the site simultaneously which will enhance the absorption of the medicine and will also decrease the burden of repeated exposures to medicines.²² Alongside this, we need tend to incorporate, use of photo bio modulation along with dry needling strategies at this time, it will enhance the healing process at the site if ulcer to twice or thrice times since it will provide a cumulative and time efficient effect over the area concerned.²⁴

Another great importance of administering useful techniques simultaneously will be lesser involvement of healthcare professionals with the same patients repeatedly and will provide patients and the professionals with utmost time and treatment plan which will benefit patients in getting same amount of treatment and interventions in lesser time and quality of treatment can be preserved. Along with this, there can be formulation of a cumulative multi modal approach which will enhance the outcome the patients and will encourage the patients to get better quality within a compound and constricted budget, which will directly reduce the financial burden over the family or care giver of the patients. Hence, promotion of rehabilitative measures for such patients which will use expertise of various medical professionals which develop strategic decisions for more such diseases in future.

REFERENCES:

- 1. Sen CK. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. Adv Wound Care (New Rochelle). 2021 May;10(5):281-292. doi: 10.1089/wound.2021.0026. PMID: 33733885; PMCID: PMC8024242.
- 2. Holl J, Kowalewski C, Zimek Z, Fiedor P, Kaminski A, Oldak T, Moniuszko M, Eljaszewicz A. Chronic Diabetic Wounds and Their Treatment with Skin Substitutes. Cells. 2021 Mar 15;10(3):655. doi: 10.3390/cells10030655. PMID: 33804192; PMCID: PMC8001234.

ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

- 3. Louiselle AE, Niemiec SM, Zgheib C, Liechty KW. Macrophage polarization and diabetic wound healing. Transl Res. 2021 Oct;236:109-116. doi: 10.1016/j.trsl.2021.05.006. Epub 2021 Jun 2. PMID: 34089902.
- 4. Jere SW, Houreld NN, Abrahamse H. Role of the PI3K/AKT (mTOR and GSK3β) signalling pathway and photobiomodulation in diabetic wound healing. Cytokine Growth Factor Rev. 2019 Dec;50:52-59. doi: 10.1016/j.cytogfr.2019.03.001. Epub 2019 Mar 12. PMID: 30890300.
- 5. Bowers S, Franco E. Chronic Wounds: Evaluation and Management. Am Fam Physician. 2020 Feb 1;101(3):159-166. PMID: 32003952.
- 6. Broussard KC, Powers JG. Wound dressings: selecting the most appropriate type. Am J Clin Dermatol. 2013 Dec;14(6):449-59. doi: 10.1007/s40257-013-0046-4. PMID: 24062083.
- 7. Ahluwalia R, Maffulli N, Lázaro-Martínez JL, Kirketerp-Møller K, Reichert I. Diabetic foot off loading and ulcer remission: Exploring surgical off-loading. Surgeon. 2021 Dec;19(6):e526-e535. doi: 10.1016/j.surge.2021.01.005. Epub 2021 Feb 26. PMID: 33642205.
- 8. Rekha PD, Rao SS, Sahana TG, Prabhu A. Diabetic wound management. Br J Community Nurs. 2018 Sep 1;23(Sup9):S16-S22. doi: 10.12968/bjcn.2018.23.Sup9.S16. PMID: 30156875.
- 9. Barros NR, Ahadian S, Tebon P, Rudge MVC, Barbosa AMP, Herculano RD. Highly absorptive dressing composed of natural latex loaded with alginate for exudate control and healing of diabetic wounds. Mater Sci Eng C Mater Biol Appl. 2021 Feb;119:111589. doi: 10.1016/j.msec.2020.111589. Epub 2020 Sep 30. PMID: 33321634.
- 10. Maranna H, Lal P, Mishra A, Bains L, Sawant G, Bhatia R, Kumar P, Beg MY. Negative pressure wound therapy in grade 1 and 2 diabetic foot ulcers: A randomized controlled study. Diabetes Metab Syndr. 2021 Jan-Feb;15(1):365-371. doi: 10.1016/j.dsx.2021.01.014. Epub 2021 Jan 23. PMID: 33524646.
- 11. Andrade SM, Santos IC. Hyperbaric oxygen therapy for wound care. Rev Gaucha Enferm. 2016 Jun;37(2):e59257. English, Portuguese. doi: 10.1590/1983-1447.2016.02.59257. PMID: 27410674.
- 12. He S, Wen H, Yao N, Wang L, Huang J, Li Z. A Sustained-Release Nanosystem with MRSA Biofilm-Dispersing and -Eradicating Abilities Accelerates Diabetic Ulcer Healing. Int J Nanomedicine. 2023 Jul 19;18:3951-3972. doi: 10.2147/IJN.S410996. PMID: 37489140; PMCID: PMC10363391.
- 13. Paschou SA, Stamou M, Vuagnat H, Tentolouris N, Jude E. Pain management of chronic wounds: Diabetic ulcers and beyond. Maturitas. 2018 Nov;117:17-21. doi: 10.1016/j.maturitas.2018.08.013. Epub 2018 Sep 5. PMID: 30314556.
- 14. Dos Santos Mendes-Costa L, de Lima VG, Barbosa MPR, Dos Santos LE, de Siqueira Rodrigues Fleury Rosa S, Tatmatsu-Rocha JC. Photobiomodulation: systematic review and meta-analysis of the most used parameters in the resolution diabetic foot ulcers. Lasers Med Sci. 2021 Aug;36(6):1129-1138. doi: 10.1007/s10103-020-03192-y. Epub 2020 Nov 15. PMID: 33190161.
- 15. Karkada G, Maiya GA, Houreld NN, Arany P, Rao Kg M, Adiga S, Kamath SU, Shetty S. Effect of photobiomodulation therapy on inflammatory cytokines in healing dynamics of diabetic wounds: a systematic review of preclinical studies. Arch Physiol

ISSN: 0975-3583, 0976-2833

VOL13, ISSUE 7, 2022

- Biochem. 2023 Jun;129(3):663-670. doi: 10.1080/13813455.2020.1861025. Epub 2020 Dec 28. PMID: 33370535.
- 16. Lawson D, Petrofsky JS. A randomized control study on the effect of biphasic electrical stimulation in a warm room on skin blood flow and healing rates in chronic wounds of patients with and without diabetes. Med Sci Monit. 2007 Jun;13(6):CR258-63. PMID: 17534231.
- 17. Hitchman LH, Totty JP, Raza A, Cai P, Smith GE, Carradice D, Wallace T, Harwood AE, Chetter IC. Extracorporeal Shockwave Therapy for Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis. Ann Vasc Surg. 2019 Apr;56:330-339. doi: 10.1016/j.avsg.2018.10.013. Epub 2018 Nov 26. PMID: 30496896.
- 18. Qureshi AA, Ross KM, Ogawa R, Orgill DP. Shock wave therapy in wound healing. Plast Reconstr Surg. 2011 Dec;128(6):721e-727e. doi: 10.1097/PRS.0b013e318230c7d1. PMID: 21841528.
- 19. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018 Jan;1411(1):153-165. doi: 10.1111/nyas.13569. PMID: 29377202; PMCID: PMC5793889.
- 20. Lindberg K, Møller BS, Kirketerp-Møller K, Kristensen MT. An exercise program for people with severe peripheral neuropathy and diabetic foot ulcers a case series on feasibility and safety. Disabil Rehabil. 2020 Jan;42(2):183-189. doi: 10.1080/09638288.2018.1494212. Epub 2018 Oct 7. PMID: 30293458.
- 21. Gunton JE, Girgis CM, Lau T, Vicaretti M, Begg L, Flood V. Vitamin C improves healing of foot ulcers: a randomised, double-blind, placebo-controlled trial. Br J Nutr. 2021 Nov 28;126(10):1451-1458. doi: 10.1017/S0007114520003815. Epub 2020 Sep 28. PMID: 32981536.
- 22. Nagoba B, Rawal C, Davane M. Citric acid treatment of a diabetic leg ulcer infected with meticillin-resistant *Staphylococcus aureus*. J Wound Care. 2022 May 2;31(5):432-434. doi: 10.12968/jowc.2022.31.5.432. PMID: 35579314.
- 23. Venkataraman K, Tai BC, Khoo EYH, Tavintharan S, Chandran K, Hwang SW, Phua MSLA, Wee HL, Koh GCH, Tai ES. Short-term strength and balance training does not improve quality of life but improves functional status in individuals with diabetic peripheral neuropathy: a randomised controlled trial. Diabetologia. 2019 Dec;62(12):2200-2210. doi: 10.1007/s00125-019-04979-7. Epub 2019 Aug 29. PMID: 31468106; PMCID: PMC6861346.
- 24. Coppola A, Montalcini T, Gallotti P, Ferrulli A, Pujia A, Luzi L, Gazzaruso C. A Comprehensive Therapeutic Patient Education May Improve Wound Healing and Reduce Ulcer Recurrence and Mortality in Persons With Type 2 Diabetes. Can J Diabetes. 2023 Feb;47(1):73-77. doi: 10.1016/j.jcjd.2022.08.004. Epub 2022 Aug 23. PMID: 36154986.
- 25. Tsourdi E, Barthel A, Rietzsch H, Reichel A, Bornstein SR. Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus. Biomed Res Int. 2013;2013:385641. doi: 10.1155/2013/385641. Epub 2013 Apr 7. PMID: 23653894; PMCID: PMC3638655.