AN OVERVIEW ON THE ROLE OF CONTINUOUS ULTRASOUND THERAPY IN IMPROVING BLOOD FLOW IN PATIENTS WITH DIABETIC FOOT

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Abstract:
Diabetic patients frequently require hospital admission due to foot issues, which also frequently result in amputations. Approximately 6% of diabetics have foot disease, which can involve ulceration, infection, or degeneration of the foot's tissues. It may have an adverse effect on a patient's livelihood, social engagement, and quality of life. Amputations are necessary for 0.03% to 1.5% of diabetic foot patients. The majority of amputations begin with ulcers, which can be avoided with proper foot hygiene and screening to determine the likelihood of foot problems. Ultrasound (US) is a noninvasive, multifunctional tool that has gained popularity in almost all medical fields recently. It may be used for both diagnostic and interventional purposes. US can identify specific indications related to diabetic foot syndrome (DFS) by being used in screening, and follow-up of the blood vessels affection which represent an important part of the pathogenesis. Regarding ultrasound use in the treatment process, high-frequency sound waves are employed for both heating and mechanically vibrating the tissues. Numerous therapeutic objectives, including tissue repair, pain management, and wound healing, have been achieved by its use. It's crucial to maintain enough blood flow to the affected areas when diabetes patients have foot issues like diabetic foot ulcers or peripheral vascular disease in order to support tissue viability and wound healing. Perhaps improving blood flow and promoting healing is the aim of this continuous ultrasonography therapy.

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Introduction

Diabetes and hyperglycemia are linked metabolic disorders. In the twenty-first century, this medical condition is spreading quickly around the world. According to predictions made by the International Diabetes Federation, the number of individuals with diabetes is expected to rise from 387 million to 592 million over the course of the next 20 years. Diabetes patients may have blood vessel and nerve damage, which can result in problems with their feet. This issue might lead to an infection and leg ulcer that would eventually require amputation. It is thought to be one of the risky situations. [1]

Lower extremity artery disease is one of the most frequent causes of diabetic foot (LEAD). LEAD is a consequence of systemic atherosclerosis and is linked to serious problems with the heart, legs, and brain system. A partial or total blockage of one or more lower leg arteries is the cause. Diabetes increases the risk of developing LEAD by four to five times in comparison to non-diabetics. [2]

Therapeutic ultrasound has been studied for a range of medical applications for more than 70 years. Continuous ultrasound (CUS) is a deep-penetrating agent that transfers energy through sound waves to have a therapeutic effect. A mechanical wave's CUS is any frequency range that is more than 20 kHz. As these cyclic waves pass through a substance, mechanical forces are produced. Numerous aspects of ultrasound, such as frequency, duty cycle, wavelength, energy, power, and intensity, influence the range of medical uses. The exchange of nutrients, heat, cavitation, microstreaming, and oxygenation are among the biological effects of the CUS. [3]

It was discovered that CUS treatment helps improve blood flow in diabetic individuals. Ultrasound is thought to have the ability to promote tissue oxygenation, increase blood flow to the afflicted regions, and enhance vasodilation through its mechanical vibrations and heat effects. [4]

I.Diabetic foot

Foot ulcers are among the most frequent and dangerous side effects of diabetes mellitus. Between 12% and 25% of diabetics may need hospitalization at some time in their life because of foot problems. Despite the availability of effective pharmaceutical and surgical therapies, they continue to be the leading cause of hospitalization and lower limb amputations associated to diabetes. Numerous supplemental and adjuvant medicines have been developed in an effort to enhance outcomes. [5]

Peripheral neuropathy and/or peripheral artery disease (PAD), foot deformities, and a history of ulceration or amputation of the toes or a portion of the foot are important risk factors for developing foot issues in diabetes. It is believed that 25–44% of individuals with foot problems have neuropathy, 10% have ischemia, and 45–60% have neuro-ischemic foot problems, which are a combination of the two. Infection is often the final consequence leading to presentation. [6]

II. Pathophysiology of diabetic foot

The pathologic mechanisms of DFU are explained by three different theories. These three include neuropathy resulting from foot damage, vascular insufficiency, and subsequent infection. [7]

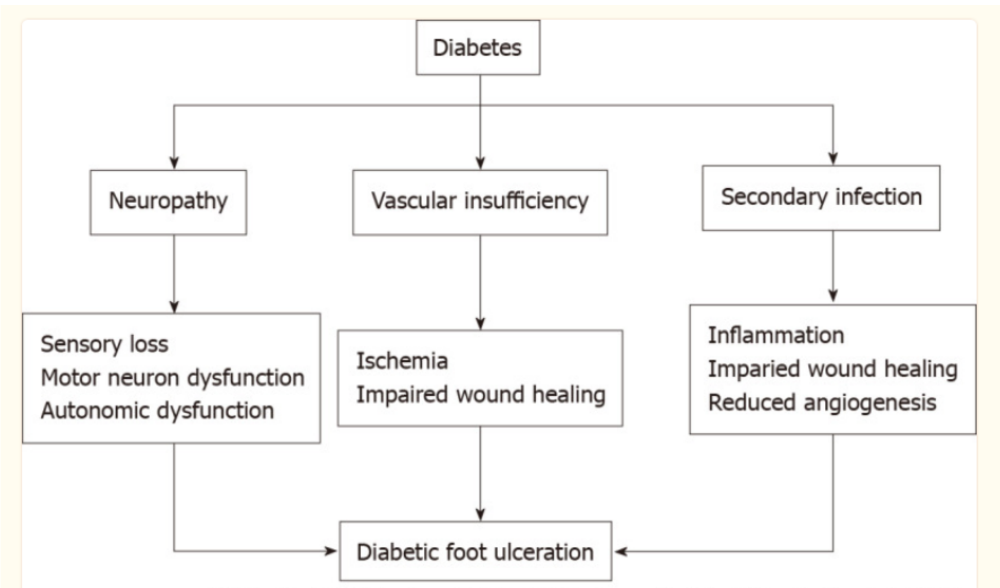

Figure (1): Diabetic foot ulcer pathophysiology. [8]

Patients with diabetes are more vulnerable to cuts and ulcers because they lack a protective feeling in their feet. The overexpression of sorbitol dehydrogenase and aldose reductase, which is caused by hyperglycemia and increases fructose and sorbitol production, is what causes this sensory impairment. [9]

The buildup of these glucose products causes osmotic stress, which in turn decreases myoinositol synthesis and neural transmission in nerve cells. Furthermore, advanced glycation end-products (AGEs) need to be taken into account from a pathogenic perspective. When glucose and dicarbonyls combine, non-enzymatic proteins, amino acids, and DNA adducts known as AGEs are produced. Diabetes raises the creation of AGEs, which is connected to the disease's complications developing. [10]

Diabetes-related neuronal autonomic dysfunction can cause sensory neuropathy as well as decreased sweating, increased dryness, skin cracking, and fissuring of the foot. Additionally, muscle atrophy and abnormalities in the architecture of the foot may result from motor neuron loss. This raises the risk of ulceration by causing focally raised pressures in different plantar foot zones. [11]

One important way that DFU progresses has been identified as impaired wound healing. Significantly, molecular alterations at the DFU site occur before the tissue anomalies that are visible to the naked eye. Significant changes to the extracellular matrix (ECM) are also important in maintaining the non-healing DFU, in addition to inflammation. [12]

Impaired angiogenesis is one of the primary reasons of the disruption in diabetic wound healing. VEGF-20 and FGF-2, two molecules that encourage angiogenesis, are reduced in DFU instances. Basically, FGF-2 promotes the migration of new blood vessels via the extracellular matrix (ECM), whereas VEGF starts angiogenesis and promotes endothelial cell proliferation. [13]

Patients with a history of diabetes for an extended period of time are more prone to have foot musculoskeletal problems, which raise the risk of ulcers. Reduced collagen breakdown, diabetic microangiopathy, and elevated glycosylation of collagen in the periarticular tissue (joint capsule, ligaments, and epidermis) are important underlying variables. [14]

III. Importance of blood flow in wound healing

Blood flow is necessary for wounds to heal. When a wound appears, the afflicted region's blood vessels go through many processes that are essential to the healing process. Blood carries oxygen and essential nutrients like glucose and amino acids to the location of the lesion. While oxygen is necessary for energy production and cell metabolism, nutrients are required for tissue repair, collagen creation, and cell growth. [15]

Blood flow facilitates the removal of waste products from the wound region, including carbon dioxide and other metabolic wastes. Effective waste product removal avoids buildup, which might impede the healing process and result in tissue damage or infection. [16]

Blood flow carries immune cells like neutrophils, macrophages, and lymphocytes to the site of the wound. These cells are necessary for infection prevention, debris elimination, and tissue regeneration. Enough blood flow ensures that immune cells get at the site promptly, bolstering the body's defenses. [17]

Collagen is a crucial component of the extracellular matrix that provides healing tissues with structural stability. Blood flow supplies the amino acids and growth hormones needed for collagen synthesis and remodeling. Optimal blood flow promotes the deposition and arrangement of collagen fibers, leading to the creation of more robust and functional tissue. [18]

Blood flow initiates the process of angiogenesis, which is the formation of new blood vessels. This is necessary for the growth of granulation tissue, a rich, vascularized connective tissue that covers the wound bed. Granulation tissue functions as a scaffold for cell migration, promotes wound contraction, and speeds up the healing process. [19]

The flow of blood aids in controlling the wound site's temperature. Sufficient blood flow facilitates the dissipation of heat produced during the inflammatory response and upholds the ideal temperature for cellular functions. Controlling the temperature properly creates the ideal environment for tissue healing and cellular growth. [20]

IV. Role of Physical therapy in Diabetic Foot Problems

Wound healing is an energy-intensive procedure that frequently needs its support. Physical therapy plays an important role in diabetic foot management. This role can help to promote and accelerate the healing process by reducing time that the implant takes to absorb and hastening the healing process. Alternative physical therapy options promote wound healing through a number of biochemical pathways and focuses on changes in the chronic wound microenvironment.

Shockwave treatment, electrical stimulation (ES), extremely low-frequency magnetic field stimulation, and photobiomodulation therapy (PBMT) are the cornerstones of energy-based physical therapy for DFU. Both PBMT and ES are frequently used in therapeutic contexts. [21]

- **Continuous ultrasound therapy**

CUS treatment is a therapeutic approach that treats a variety of tissues and ailments by applying high-frequency sound waves. It entails using a portable ultrasound equipment that continuously generates sound waves at a certain frequency. [22]

Treatment for CUS works in a few different ways. Sound waves piercing the tissues can cause mechanical vibrations that can activate cells and increase tissue temperature. This may lead to vasodilation, increased blood flow, increased metabolic activity, and enhanced tissue repair processes. [23]

When sound waves travel through a homogeneous environment, they transform into thermal energy. Sound waves with a frequency higher than human hearing are used in ultrasound. One effective deep-heating method that can heat skin up to one centimeter or more is ultrasound. Ultrasound therapy typically employs sound waves with amplitude densities ranging from 0.1 to 3 w/cm^2 and frequencies between 1.0 and 3.0 MHz. [24]

Vasodilatation, enhanced cell permeability, increased metabolism, fibroblast proliferation, release of vascular endothelial growth factor, increased collagen flexibility, and decreased edoema through increased interstitial fluid flow are a few of the hypothesised mechanisms of action of ultrasound. Together, these activities facilitate quicker wound healing. [25]

Ultrasound therapy cannot be performed on a woman who is pregnant, has a malignant lesion, or has an implant made of plastic or metal. Furthermore, patients with hemorrhagic diathesis, cardiac pacemakers, severe infections, or decompensated heart failure should not employ this treatment method. [26]

The various categories of ultrasound therapy include frequency, intensity, pulsed or continuous delivery, and tissue-contact or contact-free administration. Ultrasound causes cavitation effects in the tissue when used for debridement; at high dosages, this might lead to an unstable degree of cavitation. [27]

Low-frequency contact, also known as contact-free ultrasonic therapy, stimulates the fibroblast cell membrane and induces the fibroblasts to proliferate by synthesizing DNA, eliciting VEGF and interleukin-8 (IL-8) in the osteoblasts. Ultrasound therapy's heat impact is lessened and its debridement effect is more noticeable when applied to musculoskeletal disorders at low frequencies, such as 20–40 kHz; concurrent antibacterial and wound healing effects have also been noted. [28]

Contact-free low-frequency ultrasound is a recently developed ultrasonic technique that may promote wound healing by stimulating fibroblast proliferation and releasing VEGF and IL-8, which in turn inhibits the growth of germs in chronic wounds. Three times a week, contact-free low-frequency ultrasound treatment seems to be the most successful in shrinking the area of the wound. [29]

The most effective method for reducing the size of the wound appears to be contact-free low-frequency ultrasound therapy administered three times per week. [30]

- **Applications of Continuous Ultrasound Therapy on Diabetic Foot Complications**

1. Effects on Tissue Regeneration

Minutes after the injury is sustained, the complex process of healing gets under way. Acute inflammation, angiogenesis, proliferation, development of new tissue, and remodelling are all involved. Many coordinated cellular and molecular responses control the healing process. [31]

Treatment with CUS has been shown to stimulate cell division in a number of different tissues. The mechanical vibrations and thermal effects of ultrasonic waves can stimulate and multiply fibroblasts, endothelial cells, and other cell types involved in tissue regeneration. Accelerated cell proliferation can promote the formation of new tissue and speed up the healing process. [32]

Collagen is a vital component of the extracellular matrix that provides structural support to tissues. Continuous ultrasonic therapy has been found to increase collagen formation by fibroblasts, leading to the deposition of new collagen fibers. This might help injured or weakened tissues heal and regenerate. [33]

Usual consequence of tissue regeneration is inflammation. It has been found that the production of pro- and anti-inflammatory cytokines is regulated by continuous ultrasonic therapy, which in turn modifies the inflammatory response. This can help create an environment that is favorable for tissue regeneration by reducing excessive inflammation and encouraging a balanced immune response. [34]

Following the inflammatory phase, neighbouring cells migrate and proliferate to the injured region, angiogenesis occurs, and matrix formation occurs.

Elevated nitric oxide (NO) levels enhance vasodilation, blood flow, oxygenation, and nutritional availability. The increased blood flow facilitates the migration of macrophages into the site of damage, so aiding in the regulation of acute inflammation. [35]
Angiogenesis is necessary for both tissue regeneration and wound healing. Continuous ultrasound therapy has been shown to increase the synthesis of growth factors, such as VEGF (vascular endothelial growth factor), which in turn encourages the formation of new blood vessels. Increased angiogenesis can improve blood flow to the regenerated tissue, which facilitates the distribution of oxygen and nutrients. [36]
The generation of collagen, the management of the inflammatory response, angiogenesis, and cell proliferation can all be enhanced by continuous ultrasound treatment. Together, these mechanisms have the potential to expedite the healing of wounds, leading to their closure and the formation of robust granulation tissue. [31]

2. Pain control

One of the main clinical issues is managing chronic pain. The intricate process of acute pain may be broken down into three fundamental phases: chemical stimulus and synaptic events that are converted into electrical events in the neurons; electrical events that are transduced into chemical events at the synapse; and stimulus conversion to chemical signal. Chronic pain may result from any area of this pathway that is repeatedly and uncontrollably activated. [37]
Pain associated with musculoskeletal problems can be reduced with CUS treatment by increasing local temperature, vasodilation, and metabolism. The US is a useful treatment for soft tissue pain that may be used alone or in conjunction with other therapies. [38]
There have been reports of quick analgesic results from CUS treatment. Pain signals can be modulated by the mechanical vibrations produced by ultrasonic waves, which can excite sensory nerve endings. As a result, you could have brief pain alleviation both during and after the ultrasound therapy. [39]
Increased tissue temperature brought on by ultrasonic energy absorption has the potential to improve blood circulation and vasodilation. The heat produced has the ability to ease pain brought on by tense or stiff muscles, relax muscles, and lessen muscular spasms. [40]
The pain management gate control hypothesis may be utilized by CUS treatment. This hypothesis states that painful feelings can be interfered with and overridden by the activation of non-painful sensory signals, such as the mechanical vibrations produced by ultrasound. This may cause a brief decrease in the sense of pain. [37]
It has been discovered that CUS treatment increases the body's natural painkilling chemical production of endogenous opioids. When endogenous opioids, like endorphins, attach to opioid receptors in the central nervous system, pain is reduced and an individual feels better. [41]
US stimulation is able to actively regulate the peripheral and central nervous systems in addition to having a major impact on the activity, suppression, and proliferation of neurons. The neurological system's stimulation by the US can have both immediate and long-term impacts. Hippocampus neurons are directly activated by brief US stimulation, which also regulates the conversion of the neuronal signal into synaptic sodium and calcium channels. [38]

3. Effectiveness in Thrombosis

The US is beneficial for both articular and deep vein thrombolysis, according to a number of studies. It has been demonstrated that both high- and low-intensity ultrasound is helpful for fibrinolysis and clot thrombolysis. While low intensity US stimulates urokinase and streptokinase to gradually dissolve blood clots, high intensity US uses the heat and cavitation capabilities of US to ablate the clots. [42]
The possibility that CUS might improve thrombolytic agent penetration into the clot has been studied. The fibrin meshwork of the clot may be partially disrupted by the mechanical vibrations produced by ultrasonic waves, which will improve the diffusion and distribution of thrombolytic medications inside the clot structure. [43]
Another strategy that has been investigated is thrombolysis aided by microbubbles. It is possible to introduce tiny, gas-filled bubbles called microbubbles into the circulation. These microbubbles have the ability to oscillate and facilitate the breaking of blood clots when subjected to ultrasonic frequencies. The thrombolytic impact can be improved and the necessary ultrasonic waves for microbubble activation can be produced with continuous ultrasonography treatment. [42]

4. Continuous Ultrasound effect on Blood Flow

High intensities of heat are generated when the ultrasonic pulse is absorbed by the tissue. When enough of the wave's mechanical qualities are applied, a sizable volume of fluid is moved and microbubbles are created. The US is beneficial for both articular and deep vein thrombolysis, according to a number of studies. It has been demonstrated that both high- and low-intensity ultrasound is helpful for fibrinolysis and clot thrombolysis. While low intensity US stimulates urokinase and streptokinase to gradually dissolve blood clots, high intensity US uses the heat and cavitation capabilities of US to ablate the clots. This could promote the healing of injured tissue, making it a target for healing methods. [44]

It was demonstrated that in T2DM patients, 1 MHz US continuous and pulsed waveforms enhanced endothelium-dependent vasodilation. Because type 2 diabetes patients have higher than normal amounts of oxygen reactive species (ROS), particularly O2, endothelial damage occurs. Nitric oxide (NO) has a strong affinity for O2, which reduces its bioavailability and produces peroxynitrite. [45]

Because peroxynitrite reacts so readily with biological molecules, it can be hazardous because it can set off a vicious cycle that produces more ROS than NO. In addition to producing too much oxygen, hyperglycemia inhibits glycolytic enzymes, which leads to the accumulation of glycolytic metabolites. Because of the increased NADPH consumption, oxidative stress and endothelial dysfunction rise. The primary intracellular antioxidant that must regenerate is reduced glutathione. [46]

Microcirculatory dysfunction, end-organ hypoperfusion, hypertension, and the activation of platelets and coagulation factors are all caused by endothelial dysfunction. Over time, these activations increase the risk of coronary artery disease and atherosclerosis in patients with type 2 diabetes.[47]

Figure (2): Diabetic foot ulcer management by US [48]

An earlier investigation showed that endothelium-dependent vasodilation improved, but that wave forms did not alter. Experiments with varying intensities of continuous waveform (490 kHz, 0.21, 0.35, 0.48 W/cm2 SPTA, 10 min) showed a progressive increase in NO production, suggesting that the effect is intensity-dependent. The pulsed wave type (2.9 kHz, 30% duty cycle, 1.4 W/cm^2 SATA) improved the vasodilation that is reliant on the endothelium in humans. [49]

The pressure, intensity, and heat of mechanical waves are among the processes that have been suggested to explain how CUS affects endothelial function. The thermal effect results from ultrasonic waves being absorbed by the tissue, especially when the waveforms are continuous. [44]

CUS wave pressure may cause transient membrane holes, altered intercellular permeability, and cytoskeleton fiber remodeling. These modifications lead to the production of NO by uncoupling eNOS and increasing permeability to Ca^{2+} ions. The combination of these mechanisms results in better endothelium-dependent vasodilation in patients with type 2 diabetes. [45]

Technique

The duration of each continuous ultrasound therapy session can vary but is typically in the range of 5 to 15 minutes. The exact time may depend on factors such as the treatment area size, the specific ultrasound device being used, and the patient's tolerance. [38]

The frequency of continuous ultrasound therapy sessions can vary depending on the patient's needs and the healthcare professional's judgment. Typically, treatments may be administered several times per week initially and then gradually reduced as the condition improves. For diabetic foot patients, a common treatment frequency is 2 to 3 sessions per week, but this can vary based on individual factors. [23]

The number of continuous ultrasound therapy treatments required for diabetic foot patients can vary depending on the specific condition being treated and the individual response to therapy. In some cases, a course of treatment may consist of several weeks or months. The exact number of treatments needed will be determined by the healthcare professional based on the patient's progress and treatment goals. [26]

Selecting the right ultrasonic probe is crucial. Depending on how deep the boats being investigated are. Generally speaking, no vessel can be completely inspected by the US if the incorrect or insufficient depth is selected. Examining deeply entrenched veins in the belly, distal thigh, and proximal region of the calf requires the use of a low-frequency probe operating between 3.5 and 6 MHz, even a convex array. [27]

A 7.5 MHz probe or higher linear array can be used to study the superficial arteries that enter the proximal section of the thigh (femoral bifurcation, proximal SFA, and deep femoral artery) and the distal portion of the calf (distal crural artery).. [26] Ultrasonic probes operating at 7.5 MHz can be used also to evaluate the plantar arch, the posterior tibial artery (PTA) bifurcation, the medial and lateral plantar arteries, and their link to the dorsalis pedis at the foot level. The forefoot and digital arteries can be examined with a very high frequency probe (over 20 MHz) designed for dermatological purposes. [28]

A gel pad or other specialized tool can help improve the contact between the probe and the bone surface in cases where there are serious wound lesions at any level or where superficial arteries flow across the surface of the foot. [32]

The purpose of using ultrasound contrast agents (CEUS) to assess peripheral artery disease (PAD) was either to increase the diagnostic precision of vascular arterial mapping or to examine physiopathology and muscle reserve in individuals who were either normal or had a clinical suspicion of PAD. [23]

Conclusion

Diabetes mellitus-related injuries require a comprehensive approach. Techniques from physical therapy and rehabilitation could be included. Continuous ultrasonography treatment may help diabetic patients who have foot problems by improving blood flow and vascular health.

It has been shown that nitric oxide, a strong vasodilator, is released when an ultrasound therapy is administered. Continuous ultrasonography therapy may help collateral circulation, or the formation of new blood flow channels, when the primary blood arteries are compromised. Because ultrasound therapy promotes angiogenesis and increases blood flow, it may improve foot circulation.

References

1. Smokovski I, Smokovski I. Burden of diabetes prevalence. Managing Diabetes in Low Income Countries: Providing Sustainable Diabetes Care with Limited Resources. 2021:1-2.
2. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. Journal of clinical orthopaedics and trauma. 2021 Jun 1;17:88-93.
3. Suresh KS, Kumar S. Assessment of Diabetic Foot through the Developmental Stages of Lower Limb Abnormalities Using Ultrasound. InThe Eye and Foot in Diabetes 2020 Jul 2. IntechOpen.
4. Morishita K, Karasuno H, Yokoi Y, Morozumi K, Ogihara H, Ito T, Fujiwara T, Fujimoto T, Abe K. Effects of therapeutic ultrasound on intramuscular blood circulation and oxygen dynamics. J Jpn Phys Ther Assoc. 2014;17(1):1-7. doi: 10.1298/jjpta.Vol17_001. PMID: 25792902; PMCID: PMC4316550.
5. Monteiro‐Soares M, Boyko EJ, Jeffcoate W, Mills JL, Russell D, Morbach S, Game F. Diabetic foot ulcer classifications: A critical review. Diabetes/metabolism research and reviews. 2020 Mar;36:e3272.
6. Reardon R, Simring D, Kim B, Mortensen J, Williams D, Leslie A. The diabetic foot ulcer. Australian Journal of General Practice. 2020 May;49(5):250-5.
7. Rubitschung K, Sherwood A, Crisologo AP, Bhavan K, Haley RW, Wukich DK, Castellino L, Hwang H, La Fontaine J, Chhabra A, Lavery L. Pathophysiology and molecular imaging of diabetic foot infections. International journal of molecular sciences. 2021 Oct 26;22(21):11552.
8. Raja JM, Maturana MA, Kayali S, Khouzam A, Efeovbokhan N. Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities. World Journal of Clinical Cases. 2023 Mar 3;11(8):1684.
9. Kim J. The pathophysiology of diabetic foot: a narrative review. Journal of Yeungnam Medical Science. 2023 Oct;40(4):328.
10. Bereda G. Diabetic foot ulcer: an overview, risk factors, pathophysiology, and treatment. Curr Res Diabetes Obes J. 2022;15(4).
11. Ramachandran V, Mohanasundaram T, Karunakaran D, Gunasekaran M, Tiwari R. Physiological and Pathophysiological Aspects of Diabetic Foot Ulcer and its Treatment Strategies. Current Diabetes Reviews. 2023 Oct 1;19(8):127-39.
12. Yadav C, Srikantiah RM, Manjrekar P, Shenoy MT, Chaudhury D. Assessment of mineral pathophysiology in patients with diabetic foot ulcer. Biological trace element research. 2020 Jun;195:366-72.
13. Long I. Insight of the Pathophysiology of Diabetic Foot Ulcer. InDiabetic Foot-Recent Advances 2022 Nov 28. IntechOpen.
14. Zubair M, Ahmad J, Malik A, Talluri MR, editors. Diabetic Foot Ulcer: An Update. Singapore:: Springer; 2021 Jan 1.
15. Sharma S, Schaper N, Rayman G. Microangiopathy: Is it relevant to wound healing in diabetic foot disease?.

Diabetes/Metabolism Research and Reviews. 2020 Mar;36:e3244.
16. Burgess JL, Wyant WA, Abdo Abujamra B, Kirsner RS, Jozic I. Diabetic wound-healing science. Medicina. 2021 Oct 8;57(10):1072.
17. Balasubramanian GV, Chockalingam N, Naemi R. The role of cutaneous microcirculatory responses in tissue injury, inflammation and repair at the foot in diabetes. Frontiers in Bioengineering and Biotechnology. 2021 Sep 14;9:732753.
18. Naomi R, Fauzi MB. Cellulose/collagen dressings for diabetic foot ulcer: A review. Pharmaceutics. 2020 Sep 17;12(9):881.
19. Rai V, Moellmer R, Agrawal DK. Stem cells and angiogenesis: implications and limitations in enhancing chronic diabetic foot ulcer healing. Cells. 2022 Jul 25;11(15):2287.
20. Golledge J, Fernando ME, Alahakoon C, Lazzarini PA, Aan de Stegge WB, van Netten JJ, Bus SA. Efficacy of at home monitoring of foot temperature for risk reduction of diabetes-related foot ulcer: A meta-analysis. Diabetes/Metabolism Research and Reviews. 2022 Sep;38(6):e3549.
21. Tran MM, Haley MN. Does exercise improve healing of diabetic foot ulcers? A systematic review. Journal of foot and ankle research. 2021 Dec;14(1):1-9.
22. Uddin SM, Komatsu DE, Motyka T, Petterson S. Low-intensity continuous ultrasound therapies—a systematic review of current state-of-the-art and future perspectives. Journal of clinical medicine. 2021 Jun 18;10(12):2698.
23. Kotronis G, Vas PR. Ultrasound devices to treat chronic wounds: the current level of evidence. The International Journal of Lower Extremity Wounds. 2020 Dec;19(4):341-9.
24. Flores-Escobar S, Álvaro-Afonso FJ, García-Álvarez Y, López-Moral M, Lázaro-Martínez JL, García-Morales E. Ultrasound-assisted wound (UAW) debridement in the treatment of diabetic foot ulcer: a systematic review and meta-analysis. Journal of clinical medicine. 2022 Mar 30;11(7):1911.
25. Lázaro-Martínez JL, Álvaro-Afonso FJ, Sevillano-Fernández D, García-Álvarez Y, Sanz-Corbalan I, García-Morales E. Cellular proliferation, dermal repair, and microbiological effectiveness of ultrasound-assisted wound debridement (UAW) versus standard wound treatment in complicated diabetic foot ulcers (DFU): an open-label randomized controlled trial. Journal of Clinical Medicine. 2020 Dec 13;9(12):4032.
26. Pieruzzi L, Napoli V, Goretti C, Adami D, Iacopi E, Cicorelli A, Piaggesi A. Ultrasound in the modern management of the diabetic foot syndrome: a multipurpose versatile toolkit. The International Journal of Lower Extremity Wounds. 2020 Dec;19(4):315-33.
27. Lung CW, Wu FL, Liao F, Pu F, Fan Y, Jan YK. Emerging technologies for the prevention and management of diabetic foot ulcers. Journal of Tissue Viability. 2020 May 1;29(2):61-8.
28. Uddin SM, Komatsu DE, Motyka T, Petterson S. Low-intensity continuous ultrasound therapies—a systematic review of current state-of-the-art and future perspectives. Journal of clinical medicine. 2021 Jun 18;10(12):2698.
29. Hearne CL, Patton D, Moore ZE, Wilson P, Gillen C, O'Connor T. Effectiveness of combined modulated ultrasound and electric current stimulation to treat diabetic foot ulcers. Journal of Wound Care. 2022 Jan 2;31(1):12-20.
30. Swanson T, Hirst C, Salzman S, Frescos N. The influence of technique and type of sonotrode on debridement and patient experience using a low frequency ultrasound contact debridement device; a case series. Wound Practice & Research: Journal of the Australian Wound Management Association. 2023 Mar 1;31(1):19-27.
31. Akkus G, Sert M. Diabetic foot ulcers: A devastating complication of diabetes mellitus continues non-stop in spite of new medical treatment modalities. World Journal of Diabetes. 2022 Dec 12;13(12):1106.
32. Tan JS, Lin CC, Chen GS. Vasomodulation of peripheral blood flow by focused ultrasound potentiates improvement of diabetic neuropathy. BMJ Open Diabetes Research & Care. 2020;8(1).
33. Gnyawali SC, Sinha M, El Masry MS, Wulff B, Ghatak S, Soto-Gonzalez F, Wilgus TA, Roy S, Sen CK. High resolution ultrasound imaging for repeated measure of wound tissue morphometry, biomechanics and hemodynamics under fetal, adult and diabetic conditions. PLoS One. 2020 Nov 23;15(11):e0241831.
34. Izzetti R, Oranges T, Janowska A, Gabriele M, Graziani F, Romanelli M. The application of ultra-high-frequency ultrasound in dermatology and wound management. The international journal of lower extremity wounds. 2020 Dec;19(4):334-40.
35. Waters M, Miljkovic B, Rascon J, Gomez M, Gurovich AN. Effects of 1 MHz Therapeutic

Ultrasound on Limb Blood Flow and Microvascular Reactivity: A Randomized Pilot Trial. International Journal of Environmental Research and Public Health. 2021 Oct 30;18(21):11444.
36. Yu M, Bian Y, Wang L, Chen F. Low-intensity pulsed ultrasound enhances angiogenesis in rabbit capsule tissue that acts as a novel vascular bed in vivo. Advances in Clinical and Experimental Medicine. 2021;30(6):581-9.
37. di Biase L, Falato E, Caminiti ML, Pecoraro PM, Narducci F, Di Lazzaro V. Focused ultrasound (FUS) for chronic pain management: approved and potential applications. Neurology research international. 2021 Oct;2021.
38. Aiyer R, Noori SA, Chang KV, Jung B, Rasheed A, Bansal N, Ottestad E, Gulati A. Therapeutic ultrasound for chronic pain management in joints: a systematic review. Pain Medicine. 2020 Jul 1;21(7):1437-48.
39. Alfredo PP, Junior WS, Casarotto RA. Efficacy of continuous and pulsed therapeutic ultrasound combined with exercises for knee osteoarthritis: a randomized controlled trial. Clinical rehabilitation. 2020 Apr;34(4):480-90.
40. Todd N, McDannold N, Borsook D. Targeted manipulation of pain neural networks: The potential of focused ultrasound for treatment of chronic pain. Neuroscience & Biobehavioral Reviews. 2020 Aug 1;115:238-50.
41. Lubejko ST, Graham RD, Livrizzi G, Schaefer R, Banghart MR, Creed MC. The role of endogenous opioid neuropeptides in neurostimulation-driven analgesia. Frontiers in Systems Neuroscience. 2022 Dec 14;16:1044686.
42. Nederhoed JH, Tjaberinga M, Otten RH, Evers JM, Musters RJ, Wisselink W, Yeung KK. Therapeutic use of microbubbles and ultrasound in acute peripheral arterial thrombosis: A systematic review. Ultrasound in Medicine & Biology. 2021 Oct 1;47(10):2821-38.
43. Goudot G, Khider L, Del Giudice C, Mirault T, Galloula A, Bruneval P, Julia P, Sapoval M, Houdouin A, Tanter M, Suarez D. Non-invasive recanalization of deep venous thrombosis by high frequency ultrasound in a swine model with follow-up. Journal of Thrombosis and Haemostasis. 2020 Nov;18(11):2889-98.
44. Signori LU, Rubin Neto LJ, Jaenisch RB, Puntel GO, Nunes GS, Paulitsch FS, Hauck M, da Silva AM. Effects of therapeutic ultrasound on the endothelial function of patients with type 2 diabetes mellitus. Brazilian Journal of Medical and Biological Research. 2023 Jun 26;56:e12576.
45. Foote CA, Ramirez-Perez FI, Smith JA, Ghiarone T, Morales-Quinones M, McMillan NJ, Augenreich MA, Power G, Burr K, Aroor AR, Bender SB. Neuraminidase inhibition improves endothelial function in diabetic mice. American Journal of Physiology-Heart and Circulatory Physiology. 2023 Dec 1;325(6):H1337-53.
46. Deng P, Shi H, Pan X, Liang H, Wang S, Wu J, Zhang W, Huang F, Sun X, Zhu H, Chen Z. Worldwide research trends on diabetic foot ulcers (2004–2020): suggestions for researchers. Journal of Diabetes Research. 2022 Jan 27;2022.
47. Tuttolomondo A, Del Cuore A, La Malfa A, Casuccio A, Daidone M, Maida CD, Di Raimondo D, Di Chiara T, Puleo MG, Norrito R, Guercio G. Assessment of heart rate variability (HRV) in subjects with type 2 diabetes mellitus with and without diabetic foot: correlations with endothelial dysfunction indices and markers of adipo-inflammatory dysfunction. Cardiovascular Diabetology. 2021 Dec;20(1):1-2.
48. Turan Y, Ertugrul BM, Lipsky BA, Bayraktar K. Does physical therapy and rehabilitation improve outcomes for diabetic foot ulcers?. World journal of experimental medicine. 2015 May 5;5(2):130.
49. Adams JA, Uryash A, Lopez JR, Sackner MA. The endothelium as a therapeutic target in diabetes: a narrative review and perspective. Frontiers in physiology. 2021 Feb 23;12:638491.