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Diagnostic and Therapeutic Ultrasound on Venous and Arterial Ulcers: A Focused Review

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GENERAL PURPOSE:

To provide information about the use of ultrasound for diagnostic and therapeutic treatment of venous and arterial ulcers.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After completing this continuing education activity, you should be able to:

1. Describe the scope of the problem of peripheral vascular disease and the mechanics of ultrasound.

2. Identify research findings related to the diagnostic and therapeutic use of ultrasound for venous and arterial leg ulcers.

ABSTRACT

OBJECTIVE: To review the diagnostic and therapeutic use of ultrasound on venous and arterial ulcers.

METHODS: PubMed was searched for peer-reviewed articles using the search terms "ultrasound for venous ulcers" and "ultrasound for arterial ulcers." The search yielded 282 articles on ultrasound for venous ulcers and 455 articles for ultrasound on arterial ulcers. Data from 36 articles were selected and included after abstract review.

RESULTS: Ultrasound is an established diagnostic modality for venous and arterial disease and is indicated for wound debridement. Recent evidence continues to support its superiority over standard of care in healing venous ulcers, but findings conflict in terms of the effectiveness of low-frequency ultrasound over high-frequency ultrasound. There are currently no standardized treatment protocols for ultrasound.

CONCLUSIONS: Diagnostic ultrasound is used to assess venous and arterial disease and guide appropriate treatment for ulcers. Therapeutic low-frequency ultrasound is used to debride the wound bed, as an adjunctive topical wound treatment with standard of care, and to guide the application of other advanced therapies to chronic wounds. Better trial designs and consistent data are needed to support the effectiveness of ultrasound therapy on venous and arterial ulcers.

KEYWORDS: arterial ulcers, diagnostic ultrasound, low-frequency ultrasound, therapeutic ultrasound, ultrasound therapy, venous ulcers

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INTRODUCTION

Ultrasound is among the most frequently used imaging modalities in clinical practice.[1,2] Modern ultrasound technology was developed during World War I, when French physicist Paul Langevin created a device capable of detecting underwater submarines using high-frequency sonar.[3] Over the next few decades, many experimented with military, scientific, and industrial applications of ultrasound technology. Ultrasound as a diagnostic medical tool emerged in the early 1940s after neurologist and psychiatrist Karl Dussik of the University of Vienna and his physicist brother Friedrich used an ultrasound beam to search for brain tumors and locate the cerebral ventricles in the brain containing cerebrospinal fluid.[4] Since then, ultrasound has been used for diagnostic and therapeutic purposes in many specialties of medicine, including as an adjunctive therapy for wounds that fail to heal following standard of care (SOC).[5,6]

Globally, 202 million individuals have peripheral vascular disease, also referred to as peripheral arterial disease (PAD).[7] The disorder includes both arterial and venous insufficiency, with the latter being more prevalent. It is estimated that approximately 38 million Americans suffer from venous insufficiency, and 19.5 million have PAD.[8] The end-stage manifestation of venous and arterial insufficiency includes nonhealing wounds whose progression may lead to limb-salvage procedures, including limb loss through necessary surgical amputation. Lower-extremity ulceration is a debilitating occurrence that not only affects the patient directly but also has a great impact on the health system and the economy. Up to 1.8% of adults in industrialized nations have leg ulcers.[9,10] Chronic ulcers cost the United States $25 billion each year.[11] Venous disease is the most common causative factor for leg ulcers (contributing to up to 84% of all ulcerations),[12] and 1 of 5 people with leg ulcers have arterial disease.[13] Although most venous ulcers can heal within a year following standard compression therapy,[14] up to 70% recur, and many of them do so within 3 months of healing.[15]

For more than 4 decades, researchers, beginning with the in vivo work of Samuels et al,[16] Dyson et al,[17] and Young and Dyson,[18] have investigated the effects of ultrasound therapy on venous ulcers, noting its beneficial effects on promoting the different stages of wound healing. Today, duplex ultrasonography (DUS) is considered the first line of diagnostic assessment in venous ulcers, evaluating for both venous reflux and obstruction.[19] Early reviews of the therapeutic effects of ultrasound as applied to venous ulcers suggested a beneficial effect. However, methodological inconsistencies among the studies impeded generalizability and conclusions.[20,21] In 2010, Kloth and Niezgoda[6] reviewed the effect of ultrasound on wound healing, including venous ulcers. This article provides an updated review of the diagnostic and therapeutic use of ultrasound on venous and arterial ulcers, with a focus on the use of low-frequency ultrasound (LFUS), the current accepted therapeutic ultrasound modality for wound treatment.[6]

METHODS

The authors conducted an online search on PubMed for English-language peer-reviewed journal articles dated January 1, 2010 and later using the search terms "ultrasound for venous ulcers" and "ultrasound for arterial ulcers." The search yielded 282 articles on ultrasound treatment for venous ulcers and 455 articles for ultrasound treatment on arterial ulcers. Articles were then selected based on their relevance for ultrasound mechanism of action in wounds, diagnostic assessments for venous/arterial disease, and treatment approaches and outcomes in venous/arterial ulcers. In addition, reference lists were reviewed to ensure that all relevant evidence was included.

Data from 36 recent articles were included after review. These included 9 systematic reviews, 5 randomized controlled trials (RCTs, including 4 that evaluated the direct therapeutic effect of ultrasound), and 10 prospective studies. No articles addressed the application of ultrasound therapy to arterial ulcers.

RESULTS

Ultrasound Mechanism of Action

An ultrasound transducer applies mechanical energy via acoustic compression waves transmitted above the limit of human hearing that cause wound tissue molecules to vibrate.[5,6,22] Ultrasound dosage is based on frequency (kHz or MHz), power (in terms of intensity; W/cm^2), pulsed or continuous modes, and treatment duration.[6,9] Frequency is a key ultrasound variable. High frequencies of ultrasound have shorter wavelengths and are absorbed more easily.[6] Therefore, they are not as penetrating and are used on superficial body structures and for Doppler vascular assessment. Therapeutic-range high-frequency ultrasound (HFUS) is transmitted at a frequency of 1 to 3 MHz and is applied to wounds via direct or periwound application or by subaqueous immersion. Low frequencies penetrate deeper and are used to treat open wounds.[6] In contrast, LFUS is transmitted at a frequency of 20 to 120 kHz and is applied to wounds using a subaqueous noncontact method or light contact with saline.[5]

Acoustic cavitation and microstreaming are the 2 principal mechanisms of action of ultrasound that are crucial to the wound healing process.[5,6,22,23] Cavitation is when vibrating ultrasonic energy forms microbubbles from the dissolved gas that accumulates in its field. As the microbubbles move and compress, they cause cellular changes in wound tissue. Ultrasonic sound waves emit physical forces that displace small ions and molecules, creating microstreaming, which in turn moves fluids around and along cellular membranes. Together, cavitation and microstreaming affect cellular activity and are postulated to facilitate wound healing by reducing inflammation; promoting cellular proliferation, stimulation, and recruitment; increasing collagen synthesis and tensile strength; and promoting angiogenesis, wound contraction, and fibrinolysis.[16,22,24]

These physical energy occurrences are observed more frequently at lower kilohertz frequencies.[6,23] Transient cavitation occurs in saline with LFUS and emits energy that results in fibrinolysis and decreases bioburden, effectively debriding the wound.[5,6,25] The antimicrobial effects of LFUS in reducing bacteria and destroying biofilm have been reported by multiple in vitro studies.[5,24,26–31] In addition, some in vivo human and animal studies and clinical studies have demonstrated that LFUS destroys bacteria in the cell wall and improves healing rates in recalcitrant wounds.[5,27,30,32–35] When transmitted at 22.5, 25, or 35 kHz, the removal of necrotic tissue and reduction of bioburden in the wound bed by LFUS are as effective as surgical and mechanical debridement and are less painful, making it an optimal debridement method.[6]

In chronic venous ulcers, microcirculation is inhibited during the inflammatory phase, with increased blood flow observed during stasis.[36–40] Thermal HFUS is applied to warm tissues and stimulate perfusion.[5,6] Recent findings support the role of ultrasound in stimulating angiogenesis, collagen formation, and microcirculation during the wound healing process.[36,39] Low-intensity (30 mW/cm) pulsed ultrasound applied 3 times per week to venous ulcers resulted in a significantly higher positive labeling of collagen fibers and vascular endothelial growth factor and more CD68(+) protein cells ($P < .05$) compared with biopsied tissues of venous ulcers treated daily with 1% silver sulfadiazine.[39] In a pilot study,[36] a microlight-guide spectrophotometer evaluated the effects of LFUS applied at 34 kHz to 14 chronic venous leg ulcers (VLUs) and found that hemoglobin oxygen saturation values significantly increased for at least 30 minutes after only 1 ultrasound application ($P = .031$), indicating that LFUS resulted in improved blood oxygenation, albeit with temporary effect.

Diagnostic Ultrasound in Venous and Arterial Disease

As previously mentioned, ultrasound is the most accessible and noninvasive diagnostic imaging tool for patients with PAD and should be the first diagnostic assessment for suspected chronic venous disease.[19,41–43] The Society for Vascular Surgery and the American Venous Forum recommend that patients with risk factors and/or suspected compromised circulation undergo an arterial and venous evaluation using DUS to assess both the deep and superficial venous system for lower-extremity varicose veins, edema, or venous skin changes (Clinical, Etiology, Anatomy, Physiology clinical stage 2–6)[44] to determine the pattern(s) of incompetence prior to making treatment recommendations.[41] Unfortunately, diagnostic ultrasound is underutilized for PAD, because of clinicians' lack of training, expertise, and confidence in the technology.[45] Primary care providers sometimes do not recognize the signs and symptoms of venous insufficiency, which when left untreated result in chronic venous ulcers with high rates of ulcer recurrence.[46] The underlying pathophysiology of venous insufficiency is consequent venous hypertension.[41] It is important for physicians to attempt to rule out venous disease by asking patients about the classic symptoms of venous reflux: leg heaviness, leg fatigue, and a dull, aching discomfort that is exacerbated by prolonged leg dependence and improves with leg elevation. This is particularly important in patients with chronic venous ulcers who may not necessarily report these symptoms.

When evaluating a patient with open wounds, it is recommended that a highly experienced vascular ultrasound technician perform the examination at an outpatient wound center,[6,42,46,47] because this technology is operator dependent. Hospital radiology departments may not be the optimal DUS setting for wound care patients because of a potential lack of advanced dressing supplies or nursing staff on site to redress wounds, which can result in a limited study.

The equipment required to perform the venous ultrasound examination is simple by current standards, and the assessment is performed readily using a handheld ultrasonography probe. Gray-scale imaging, pulsed-wave Doppler, and a linear 7.0- to 15-MHz transducer are necessary elements that are found on most portable DUS units available today.[41,42,48] Color Doppler can expedite the evaluation, but it is not required, because pulsed-wave Doppler is a much more reliable and reproducible means of documenting reflux (although color flow provides superior guidance when delivering treatment such as sclerotherapy).[43,47,49] Spectral Doppler ultrasonography and color-flow vascular imaging supplement gray-scale ultrasound in identifying blood vessels, confirming the direction of blood flow, and detecting vascular stenosis or occlusion.

In general, the goals of the diagnostic ultrasound examination are to identify all incompetent truncal veins and to determine whether they are responsible for the patient's clinical problem.[41,47] When evaluating patients for reflux, the examination should be performed in the pathophysiologically appropriate standing position. Generally, the examination begins at the saphenofemoral junction.[42] The common femoral vein is evaluated for obstruction and reflux. Next, the great saphenous vein (GSV) is followed from its junction down beyond the level of any visible varicose veins. The relationship of the GSV to any abnormal veins is assessed by tracing its course and the course of any tributaries that might lead to the abnormal veins. Clinicians should be aware of the standard tributary anatomy of the GSV and able to recognize its frequent variations.[43] The anterior accessory GSV originates from the GSV just below the saphenofemoral junction and then courses obliquely down the anterior thigh, where it is often responsible for varicose veins.

Typically, DUS is used to evaluate the GSV and the small saphenous veins and their primary tributaries found within the saphenous fascia.[41,43] During axial or cross-sectional imaging, these veins resemble an "Egyptian" eye.[42] The majority of the tributaries of the GSV and small saphenous veins are unnamed and are found using imaging in the subcutaneous tissue outside the superficial fascia.[43]

Diagnosing Peripheral Arterial Disease

The ankle-brachial index (ABI) compares the brachial systolic pressure with the ankle systolic pressure and is measured to determine PAD.[50] An ABI should be obtained on patients older than 70 years, patients 50 years or older with cardiovascular risk factors, or any patient with symptoms of PAD or an abnormal lower-limb vascular examination. Patients with a normal ABI but a high suspicion for intermittent claudication should have the measurement repeated after exercise. An ABI of 1.3 or greater is attributable to incompressible vessel walls at the ankle and is nondiagnostic. Patients with an elevated ABI will need additional testing, such as Doppler waveform analysis.[49] A change in waveform from one level to the next is indicative of PAD and is highly operator dependent.

Therapeutic Use of Ultrasound on Venous Ulcers

Although the Society for Vascular Surgery, American Venous Forum, and American College of Phlebology recommend venous ultrasonography in addition to standard compressive therapy and local wound care to help improve ulcer healing and to reduce the risk of recurrence,[41,48] recent systematic reviews, including a 2017 Cochrane review that analyzed 11 RCTs, have not found reliable evidence to support the treatment of venous ulcers and prevention of ulcer recurrence rates with either LFUS or HFUS.[12,51,52] The main issue behind the low-quality evidence has been poor trial design, including small heterogeneous samples, problems with bias, imprecision, and limited data. Older but small RCTs suggest that noncontact LFUS (NLFUS) has a beneficial effect on healing ischemic, neuropathic, and venous wounds, but the strength of evidence is also very limited.[21,53]

High-frequency Versus Low-frequency Ultrasound Therapy

In the past, HFUS was targeted by clinical research,[6,17,54–61] with some studies suggesting a beneficial effect on venous ulcers[6,17,54,55,58–60] and others demonstrating no significant difference in outcomes between HFUS and sham ultrasound.[6,56,57] Complications resulting from HFUS, including burns and endothelial injury, led to its limited use in clinical practice.[61] Further, studies demonstrated that LFUS promotes wound healing better than HFUS.[6,58,61,62] A recent, large RCT conducted by Watson et al[9] investigated the weekly application of pulsed, low-dose HFUS (0.5 W/cm^2, 1 MHz) and SOC (n = 168 patients) compared with SOC alone (n = 169 patients) for up to 12 weeks on patients with at least 1 chronic VLU (>6 months' duration) greater than 5 cm^2 and without moderate to severe arterial disease (Table). Before and after adjusting for wound variables, use of compression bandaging, and the study center, there was no significant difference in time to heal between the intervention and control group, nor was there any difference between the proportion of patients with VLUs healed by 12 months, change in ulcer size at 4 weeks, recurrence rates, or quality of life. However, the HFUS group had significantly more adverse events (P = .30) than the SOC group. In a follow-up economic evaluation, the authors found that the HFUS group actually took 14.7 days longer to heal than the SOC group, had 0.009 fewer quality-adjusted life-years, and had higher treatment costs.[63] The authors did not find any therapeutic benefit of applying HFUs to recalcitrant VLUs, nor was this modality cost-effective.[9,63]

In 2004, the US Food and Drug Administration (FDA) approved NLFUS (40 kHz) therapy for use on wounds.[23,61,64,65] Older retrospective analyses demonstrated that LFUS reduced pain related to venous wounds[6,66,67] and improved healing rates in VLUs and other chronic wounds.[6,68,69] Prospective studies[6,21,23,53,70,71] including 2 VLU RCTs and 1 RCT involving ischemic wounds[52,70,71] also found that LFUS led to improved healing rates. A 2008 systematic review by Ramundo and Gray[72] did not find sufficient evidence to confirm the beneficial effect of LFUS as a debridement method, but as discussed in the section on mechanisms of action, more recent literature supports the use of LFUS in reducing bioburden, destroying biofilm, and debriding wounds.[6,24–27,32,33] In 2012, Escandon et al[33] published a small pilot study of the effect of NLFUS on venous wound healing, pain, bacterial counts, and the expression of inflammatory cytokines. After 4 weeks of treatment, there was a significant reduction in wound area (P = .0039), and decreases in pain, bacterial counts, and inflammatory cytokines were also observed, further supporting the use of LFUS for wound debridement and for facilitating the transition of the VLU from stasis, preparing the wound for the next step of the wound management process.

Previously, there were no trials that compared the effect of HFUS and LFUS on VLUs.[64] Two recent RCTs evaluated adjunctive HFUS and LFUS therapy applied 3 times weekly to VLUs with SOC alone (Table).[61,64] Both RCTs were small, with 90 participants randomized and distributed evenly across the 3 groups. Both trials included VLUs with a duration of at least 4 weeks that failed to heal after only 2 weeks of standard compression therapy.

Olyaie et al[64] compared the effectiveness of HFUS, NLFUS, and SOC (defined as multilayered compression bandaging and nonadherent dressing applied 3 times per week and sharp debridement performed twice weekly for 3 months; Table). Patients with arterial disease were excluded. The SOC group had an initial mean area of 9.60 cm^2, which decreased to 4.28 cm^2 at 4 months, a 44.6% reduction. The mean wound areas at the beginning of the study for the HFUS and NLFUS groups were 9.86 and 10.01 cm^2, respectively, which decreased to 3.23 and 2.72 cm^2 at 4 months (a reduction of 32.8% and 27.2%, respectively). These differences in wound sizes were significant (P = .04). For the SOC, HFUS, and NLFUS groups, all wounds were healed after a respective mean 8.50, 6.86, and 6.65 months (P = .001). The ultrasound groups had significant decreases in edema and pain reported at 4 months (P < .05). Although the ultrasound groups had better outcomes than the SOC group, there were no significant differences in outcomes among the patients treated with HFUS versus LFUS, although the treatment response appeared better in the LFUS group.

Beheshti et al[61] applied HFUS, LFUS, or SOC to the 3 respective study groups until the VLUs healed (Table). Patients with neuropathy, infections, PAD, and diabetes were excluded. No patient or wound characteristics were provided, but the authors noted they were well balanced among study groups. The mean time to heal was 8.13 months for the SOC group, and the HFUS and LFUS groups had significantly lower mean times to heal of 6.10 and 5.70 months, respectively (P < .001). Both ultrasound groups also had a significant reduction in wound area (P = .01), pain (P < .001), and edema (P < .0001) at 4 months, compared with the SOC group. Six months after complete wound healing, there were no significant differences in recurring VLUs among all groups. While both ultrasound groups demonstrated better wound healing outcomes compared with SOC alone, there were no significant differences between HFUS and LFUS, similar to what was observed in the study by Olyaie et al,[64] although (again) LFUS appeared to have a better response to treatment.

Other Low-frequency Ultrasound Clinical Studies

The 2 RCTs comparing LFUS with HFUS and SOC demonstrated that ultrasound therapy was more effective than SOC in healing VLUs, but did not find that LFUS was significantly more beneficial than HFUS.[61,64] A systematic review with meta-analysis and a second meta-analysis that evaluated the use of LFUS on chronic wound healing rates were published in 2011.[73,74] The systematic review included 8 RCTs that evaluated different doses of LFUS on venous and diabetic foot ulcers, suggesting a beneficial effect, especially within 5 months of application, when LFUS was applied, but the authors noted significant biases that might affect the trial data.[73] The meta-analysis included 8 studies of NLFUS and concluded that the modality consistently reduced wound area and improved healing rates.[74]

A more recent RCT by Gibbons et al[75] in 2015 evaluated NLFUS applied 3 times per week for 4 weeks versus SOC in 81 patients with demonstrated arterial flow and with VLUs with a duration greater than 30 days and an area of 4 to 50 cm^2 (Table). At 4 weeks, the mean wound area reduced by 61.6% in the NLFUS group compared with 45% in the SOC group (P = .02). The NLFUS group had significantly reduced median and absolute wound areas (P = .02 and P = .003) and pain scores (P = .01) compared with the SOC group. Therefore, a more favorable treatment response was observed with NLFUS therapy.

Table.

SUMMARY OF RECENT RCTS COMPARING ULTRASOUND THERAPY WITH SOC FOR VENOUS ULCERS

Study (n)	Ultrasound Therapy Evaluated	Mean Patient Age, y	Comorbidities Included
Watson et al[9] HFUS: 168 SOC: 169 Total: 337	HFUS	HFUS: 68.9 SOC: 69.9	PAD Intolerance toward high-compression therapy
Olyaie et al[64] HFUS: 30 NLFUS: 30 SOC: 30 Total: 90	HFUS and NLFUS	HFUS: 66.2 NLFUS: 64 SOC: 60.2	BMI, high BP, smoking status, and prior DVT or venous surgery
Beheshti et al[61] HFUS: 30 NLFUS: 30 SOC: 30 Total: 90	HFUS and NLFUS	Unknown	
Gibbons et al[75] NLFUS: 41 SOC: 40 Total: 81	NLFUS	NLFUS: 60.3 SOC: 60.0	BMI, CAD, hypertension, diabetes, anemia, pulmonary disease, kidney disease, smoking status, prior ulcer, and mean no. of ulcers

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; DVT, deep vein thrombosis; HFUS, high-frequency ultrasound; NLFUs, noncontact low-frequency ultrasound; PAD, peripheral arterial disease; QOL, quality of life; RCT, randomized controlled trial; SOC, standard of care.

A small pilot study evaluated the effect of low-intensity (<100 mW/cm^2) LFUS on 20 subjects who were randomized to receive either 20 kHz for either 15 or 45 minutes per session, 100 kHz for 14 minutes, or a sham for 15 minutes over 4 sessions.[16] Eight of the 15 ulcers (53.3%) treated with LFUS healed within 4 treatment sessions compared with 2 of the 5 (40%) in the sham group. Participants undergoing 20 kHz of LFUS for 15 minutes showed the most favorable healing rates, with a significantly faster rate of wound closure ($P < .03$), and all 5 healed by the fourth treatment session, suggesting that shorter sessions of low-dose LFUS may be more effective. Another small study compared the effect of low-dose, pulsed LFUS applied 3 times per week for 3 months with daily treatment of 1% silver sulfadiazine. The ultrasound group had mean percentage area reduction of 41% on day 90, whereas the silver sulfadiazine group did not have a decrease in area ($P < .05$). Larger RCTs are needed to confirm the findings from these small prospective studies.

Ultrasound-guided Therapy

Ultrasound is also used to guide the application of other advanced treatments to the wound. For example, ultrasound is currently used to direct endovenous ablation of deeper superficial veins and incompetent perforating veins.[41]

Ultrasound-guided foam sclerotherapy (UGFS) is an increasingly utilized endovenous ablation technique. Ultrasound-guided foam sclerotherapy combines the principles of sclerotherapy with the advantages of image guidance and is the most minimally invasive ablation technique for the elimination of superficial venous reflux and alleviation of venous hypertension[41,42,47] compared with the surgical method of flush saphenofemoral ligation with stripping (also known as high ligation and stripping [HL/S]).[76–78] For nearly 100 years, sclerotherapy has injected chemicals into the veins to obstruct them and cause endoluminal fibrosis.[41,79] Accurate identification of incompetent vein segments and their distinction from adjoining normal veins and arteries improve the success and minimize the risk associated with sclerotherapy of deeper and larger veins. The target vein can be punctured with real-time ultrasound guidance, leading to a more precise and elegant delivery of the sclerosant.[41]

Ultrasound-guided foam sclerotherapy has also been studied for its effect on healing venous wounds, although the evidence has been limited by small sample sizes and short follow-up times.[40] Nevertheless, multiple observational studies conducted in recent years support the use of UGFS on superficial venous reflux and chronic venous insufficiency to improve the healing outcomes of chronic venous ulcers, noting that this technique

Comorbidities Excluded	Mean Wound Area, cm^2	Wound Duration	Analysis of Outcomes
Poorly controlled diabetes Moderate to severe arterial disease	HFUS: 28 SOC: 27.2	HFUS: 126 (75%) >6 mo SOC: 113 (66.9%) >6 mo	No difference between times to heal, proportion of patients with ulcers healed by 12 mo, change in ulcer size, recurrence rates, or QOL HFUS had significantly more adverse events ($P = .30$)
Diabetes PAD Signs of arterial disease	HFUS: 9.9 NLFUS: 10 SOC: 9.6	Duration greater than 4 wk included	HFUS and NLFUS had significantly reduced wound areas ($P = .04$), edema, and pain ($P < .05$), and higher healing rates ($P = .001$) No significant differences among HFUS and NLFUS patients
Diabetes PAD Infection Neuropathy	Unknown	Unknown	HFUS and NLFUS had significantly less times to heal ($P < .001$), wound area reductions ($P = .01$), pain ($P < .001$), and edema ($P < .0001$) No statistical differences in recurrence rates at 6 mo No significant differences among HFUS and NLFUS patients
Infection Confounding treatments and comorbidities +5 ulcers on index limb	NLFUS: 12.1 SOC: 13.5	NLFUS: 27.0 mo (mean) SOC: 24.4 mo (mean)	NFLUS had a significantly reduced wound area at 4 wk ($P = .02$) and pain $P = .01$)

appears to be as effective as surgery, with similar recurrence rates.[40,80–83] These recent studies reported high healing rates, with 96% of venous ulcers healed at 3 months[80] and at least 79.4% healed at 6 months.[40,82] Recurrence rates at 1 and 2 years ranged from 2.3% to 8.1% and 4.9% to 14.9%, repectively.[40,80,83] However, high recanalization rates with UGFS have impacted its clinical use. Howard et al[83] recently reported recanalization rates of 39% at 1 year and 24% at 2 years.

Recently, treatment for vascular disease has relied more on endovenous thermal ablation (EVTA), which is done using radiofrequency or laser technology applied to major culprit refluxing truncal vessels and performed under local tumescent anesthesia.[41,42,47] To identify refluxing venous segments, DUS is used in patient selection for this procedure.[41] Laser and radiofrequency EVTA of the saphenous veins and their primary tributaries utilize catheters peripherally inserted into the abnormal vein and carefully advanced to the level of reflux (but far enough from the deep venous system), based on safety parameters under the guidance of ultrasound.[41] These catheters are then activated and withdrawn across the treatment segment, resulting in the permanent occlusion of the incompetent vein segments.

Ultrasound can also be used to reduce pain during these procedures by guiding tumescent anesthesia,[84,85] and ultrasound-guided femoral and sciatic nerve blocks may also considerably reduce pain during endovenous laser ablation.[86,87] As with UGFS, Cochrane systematic reviews have found laser and radiofrequency EVTA to be as effective as HL/S on varicose veins,[76,77,88] and the most recent systematic review and meta-analysis published in 2016 touts EVTA superiority over surgery and UGFS because of higher anatomical success rates (98.5% for endovenous laser ablation, 97.1% for radiofrequency ablation, 63.6% for UGFS, and 58.0% for HL/S).[89] This was further supported by an RCT published in 2016 by Venermo[78] that compared HL/S, endovenous laser ablation, and UGFS and demonstrated that 49% of patients treated with UGFS had recurrent GSV reflux at 1 year, compared with 3% treated with surgery or endovenous laser ablation. Further, although UGFS is less costly than EVTA,[90] EVTA is more cost-effective.[91] Researchers have only just begun to explore the effect of EVTA on venous ulcers.[92] Alden et al[92] studied the effect of UGFS and EVTA versus compression therapy on healing and recurrence rates in 86 patients with 95 venous ulcers. Ulcers treated with UGFS or EVTA had significantly improved healing rates (9.7% vs 4.2% per week; $P = .001$) and significantly fewer recurrences after 1 year (27.1% vs 48.9%; $P < .015$) than ulcers treated with compression therapy alone. More research is needed, however, on the effect of EVTA techniques on venous ulcers to better understand the treatment effect.

Low-frequency Ultrasound Treatment Protocol for Wounds

Low-frequency ultrasound is indicated for the debridement, irrigation, and topical treatment of venous ulcers with infection and impaired circulation and results in reduced bioburden, pain, antibiotic usage, and healing rates.[6] Wounds with systematic, advancing cellulitis; metal components; associations with electronic devices; and uncontrolled pain should be treated cautiously with LFUS. There are currently 4 LFUS devices that have been cleared by the FDA for their use on acute and chronic wounds, most notably for their debridement role.[6]

Standardized treatment parameters for LFUS in wound care are still lacking.[5] The manufacturers' recommendations for use and the FDA-cleared indications should guide facility-based LFUS protocols.[5] Ultrasound has been applied 1 to 3 times weekly in research protocols.[8] Treatment algorithms recommended by the manufacturers are generally based on longer treatment times for larger wound sizes, so that each session length is determined by the wound area.[61,64] Generally, lower doses of LFUS have been more effective in wound healing; 15 minutes of 20 kHz LFUS (633 J/cm^2) at 1-Hz pulse repetition frequency has been recommended.[16]

DISCUSSION

The role of ultrasound in diagnosing venous and arterial disease is well established. In terms of therapeutic function, in the past, HFUS was frequently studied,[6,17,54–61] but today, LFUS (NLFUS in particular) is utilized more in the wound care setting for its superior role in debriding the wound and preparing it for treatment.[61] However, inconsistent and limited evidence hinders the more widespread adoption of ultrasound therapy in clinical practice. Although LFUS appears to have a better treatment response than HFUS, recent RCTs found that, in terms of statistical significance, LFUS is no more effective than HFUS in healing venous ulcers.[61,64] However, these trials did not evaluate the safety of these modalities; adverse event and complication rates are a known issue with HFUS, hindering its clinical use.[61] Watson et al[9] found that HFUS caused significantly more adverse events than SOC, but there are no data to compare HFUS and LFUS.

Clinical practice guidelines recommend ultrasound as adjunctive therapy for chronic venous ulcers, but recent systematic reviews and meta-analyses found that the quality of evidence was lowered by limitations in trial design, including small heterogeneous trial populations, significant bias, imprecision, and limited data.[12,51,52,73] Generally, these issues continue to weaken the evidence obtained from more recent trials (Table). Among the 4 most recent therapeutic ultrasound RCTs,[9,61,64,75] although the study groups were more homogeneous, 3 had small samples. (However, the trial by Watson et al[9] is considered the largest trial evaluating therapeutic ultrasound on venous ulcers to date, with 337 patients enrolled.) Safety data continue to be very limited, with the Watson et al[9] trial, as mentioned previously, being the only one to evaluate adverse events.

The strength of evidence for ultrasound therapy is further complicated by the makeup of the patient population with venous and arterial disease. For example, when comparing UGFS with HL/S, randomization is not realistic and may not be ethical, considering the advanced age and frailty of the targeted patient populations.[40,80] Clinical research is only beginning to evaluate EVTA techniques on venous ulcers,[92] and the reality is most patients would never choose surgery over a minimally invasive procedure.[40] Therefore, one has to rethink the appropriate evidence base for these modalities.

Limitations

The limitations of this literature review are that it is a generalized, high-level review that summarizes updated information published on the diagnostic and therapeutic use of ultrasound on venous and arterial ulcers since 2010. This article is not intended to be a comprehensive, detailed systematic review. The search for articles was limited to PubMed because it is the largest online database of peer-reviewed medical articles. Because abstracts were first scanned for relevant content information, some articles with relevant information may not have been captured by the literature search.

Based on the search results, it would appear that this is the first review that attempted to cover the effect of ultrasound on arterial ulcers. A clear omission from recent literature is that, although diagnostic ultrasound is widely used to assess venous and arterial disease, no recent evidence was found for the therapeutic effect of ultrasound on arterial ulcers. This is not surprising when considering that arterial disease is often excluded from clinical trials.[61,64,75]

Although the question of appropriateness of RCTs is controversial in terms of the future directions of ultrasound research on venous and arterial wounds, what can be addressed by further study are the data and sample limitations currently weakening the evidence base. Broader study samples with more complete patient and wound data and a stronger study design that can comprehensively analyze the efficacy, effectiveness, and safety of ultrasound therapy on wounds would help to strengthen clinical findings. It is hoped that more clinicians will follow clinical practice guidelines that recommend diagnostic ultrasound for venous and arterial disease and the application of ultrasound therapy to venous ulcers so that adequate wound management can begin as soon as possible for the patient. However, standardized treatment protocols are still needed, which require a stronger evidence base. To better support the debridement and adjunctive wound healing role of LFUS, standardized parameters are also needed that better measure and report the effects of ultrasound on bioburden.[5,23]

CONCLUSIONS

Diagnostic ultrasound is used to assess venous and arterial disease and guide the appropriate treatment, including for venous and arterial ulcers. Therapeutic LFUS can effectively debride the wound bed and jumpstart the stalled healing process in a chronic wound; it is also used as an adjunctive topical wound treatment with SOC and helps guide the application of other advanced therapies in venous ulcers. Because of poor trial design and inconsistent and limited data, stronger evidence is still needed to support the effectiveness of ultrasound therapy on venous and arterial ulcers.

PRACTICE PEARLS

- Duplex ultrasound is the first line of diagnostic assessment for venous and arterial disease.
- Low-frequency ultrasound therapy is indicated for the debridement and treatment of impaired venous ulcers.
- Low-frequency ultrasound is used as adjunctive therapy to prepare the wound bed for treatment by reducing bioburden, destroying biofilm, and promoting microcirculation to transition the wound healing process from stasis.
- Ultrasound is also used to guide the application of other advanced therapies, such as sclerotherapy, to the wound.
- Standardized treatment protocols are still needed for the application of therapeutic ultrasound to the wound.

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