Cutting Edge Treatments for Diabetic Foot Management

These new products allow for early detection and care of DFUs.

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Introduction

According to the American Diabetes Association, more than 30 million Americans are diagnosed with diabetes.[1] More than 190 million people are affected worldwide, and the number is expected to reach a staggering 642 million by the year 2040.[2-4] If left untreated, many of these people can develop foot complications, such as a diabetic foot ulcer (DFU). Foot ulceration development among the diabetic population can be as high as 25%.[5] All cases with a DFU are associated with high morbidity and mortality and have a significantly higher risk of lower-extremity amputation than patients without diabetes.[6]

Many of these patients also have other underlying medical illnesses, such as peripheral vascular disease (PVD). Management of diabetic-foot complications within the United States has posed a huge economic burden.[7] As complications due to diabetes are ever increasing and have an enormous economic burden on patients and their families, early diagnosis and preventative measures are essential. In this article, we will present new technologies for early detection of diabetic foot disease, wearable technologies, and new treatments in the area of advances in wound care and limb salvage.

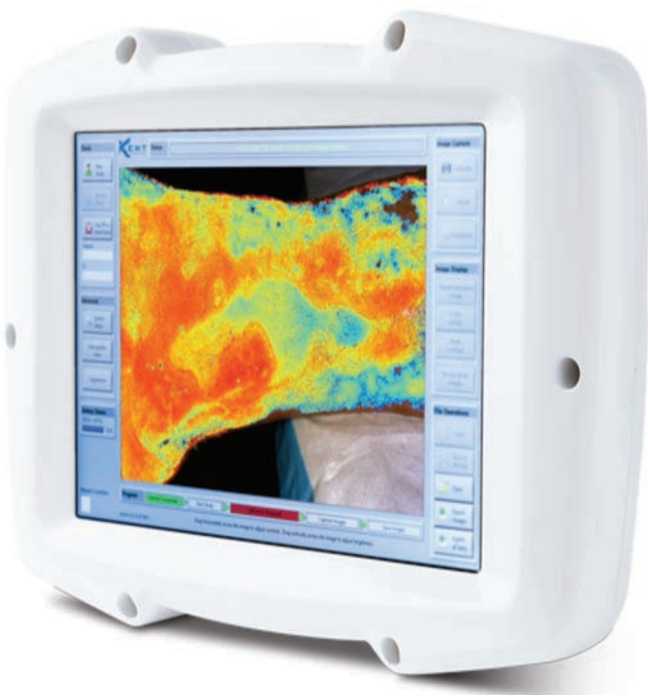

Figure 1: Kent Imaging KD203 Device—http://www.kentimaging.com/

Hyperspectral Imaging

Currently, there are several methods for evaluating perfusion to a wound and assessing vascular status. These methods include, but are not limited to, ankle-brachial index (ABI), Doppler ultrasound, transcutaneous oxygen partial pressure, and segmental limb pressures. However, because of the advanced disease process being seen, ABI and segmental limb pressures are more limited in their analysis in patients with calcified vessels. Transcutaneous oxygen partial pressures are performed on the skin adjacent to tissue loss to determine perfusion status. Early detection of vascular status allows the medical community to take a more proactive role in patient care to prevent medical complications arising from diabetes and PVD.

Hyperspectral Imaging (HSI) technology has profound implications and practical uses in the field of medicine. It has been developed as a screening tool for patients who are at risk of developing diabetic-foot ulcerations and tissue breakdown. HSI is designed to predict the development of diabetic-foot ulceration, with a high level of sensitivity and specificity before the ulcer becomes clinically apparent.[8] It constructs a spatial anatomic map of tissue oximetry based on the utilization of molecular data by analyzing oxyhemoglobin and deoxyhemoglobin levels.[9,10]

There is a growing number of such devices currently on the market and they are being evaluated for their

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role in tissue perfusion analysis. One such device by Kent Imaging (Figure 1) absorbs light in the near infrared spectrum, 700-1000nm, to make quantitative analysis of tissue perfusion within the subcutaneous arterioles and venuoles of a given tissue.[11,12] Alternatively, HyperMed's HyperView (Figure 2) utilizes wavelength of visible light, between 500-660nm, allowing measurement of the superficial capillary bed, where tissue oximetry may be different than the subcutaneous peri-wound area.[13]

Hyperspectral Imaging (HSI) technology has profound implications and practical uses in the field of medicine.

These types of devices take diagnostic images to detect the microcirculatory chang-

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Figure 2: HyperMed HyperView™ https://hypermed.com/

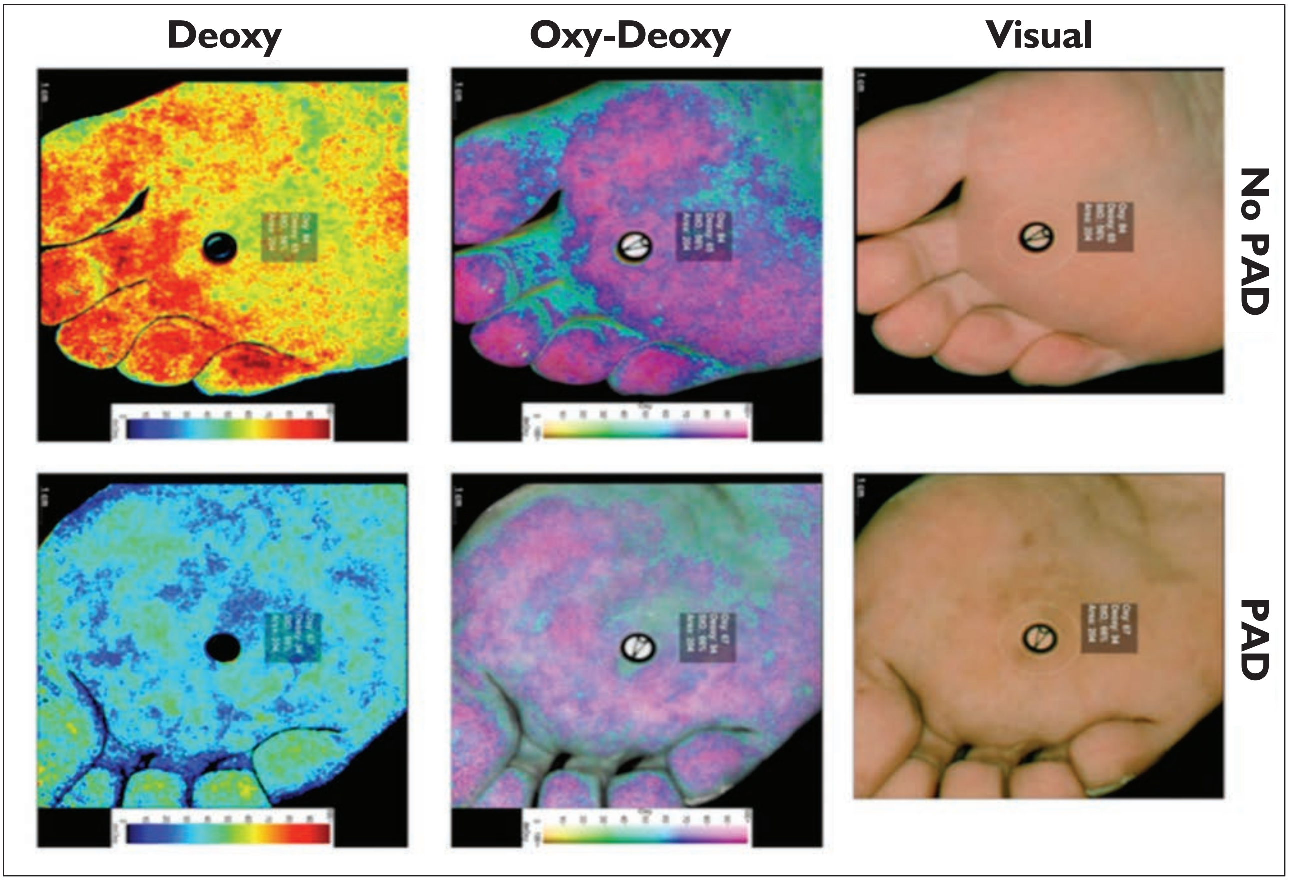

Figure 3: Visual Images from Hyper-spectral Images comparing the plantar surface of (left) foot with no PVD and (right) foot with PAD. J. A. Chin, 2011(16)

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es in a diabetic foot by monitoring perfusion to a particular tissue of interest, such as pre-diabetic ulceration sites.[14] This allows physicians to visualize local oxygen delivery and viability, as well as tissue that potentially can become ischemic. In addition to risk management of diabetic feet, a healing index can also be derived to correlate with an ulcerative site to determine healing potential based on the blood flow to the particular area of tissue.[15]

Lastly, these devices allow for early assessment and diagnosis for patients who have peripheral vascular disease PVD. The deoxyhemoglobin level has a positive correlation to the severity of PVD.[16] These devices are compact, fast, and are non-invasive, which allows them to be used in the clinic setting as well as in the operating room for immediate results to engage patients about their health before complications arise (Figure 3).

The Sudoscan allows one to measure sweat gland function at the hands and feet; thus, sudomotor function represents an area of interest in the early detection of peripheral neuropathy in at-risk diabetic patients.

Sudoscan

Diabetic peripheral neuropathy (DPN) is also an area of concern when it comes to management of the diabetic foot, as the loss of the protective sensation (LOPS) coupled by repetitive micro-trauma can lead to eventual plantar ulcerations. The ten-gram monofilament test is a quick non-invasive test used during clinical exams to assess the protective threshold. However, the monofilament test is not an objective measurable test. It can be subject to variability, and by the time of diagnosis, symptoms may already be present and irreversible. Alternative methods such as the Ipswich Touch Test have been found to perform just as well as the 10G monofilament test, but without the need of any additional testing instrumentation.[55]

Sudomotor dysfunction is one of the first and earliest detectable manifestations of neuropathy. The Sweat glands are innervated by unmyelinated sympathetic C-nerve fibers. These distal small nerve fibers are the first to be impacted by chronic hyperglycemia, which leads to abnormalities in sudomotor function.[17] The Sudoscan allows one to measure sweat gland function at the hands and feet; thus, sudomotor function represents an area of interest in the early detection of peripheral neuropathy in at-risk diabetic patients.[18] The Sudoscan quantifies its assessments based on the amount of chloride ions in sweat.[19] Early identification of sudomotor dysfunction with sudoscan allows for one to discuss blood glucose control, risk factors, and preventative measures to prevent chronic long-term complications of diabetic peripheral neuropathy, including lower extremity ulcerations.

Emerging "Smart" Technologies

Smart Socks and Smart Mat

New technologies have also expanded to consumer wearable products that can assist with prevention and early detection of lesions on the lower extremity. Embedded sensors within "smart socks" can measure skin temperature in different areas of the feet, which has been found to be an indicative measure of shear stress.[20,21] Sensors are placed in areas of high pressure on the foot that are known to lead to possible ulceration. Alterations in skin temperature precede tissue breakdown and diabetic foot ulceration development, so smart socks provides a window of opportunity to reverse potential complications before they begin by taking preventative measures.[22,23] There are also fiber-optic sensors, which can measure not

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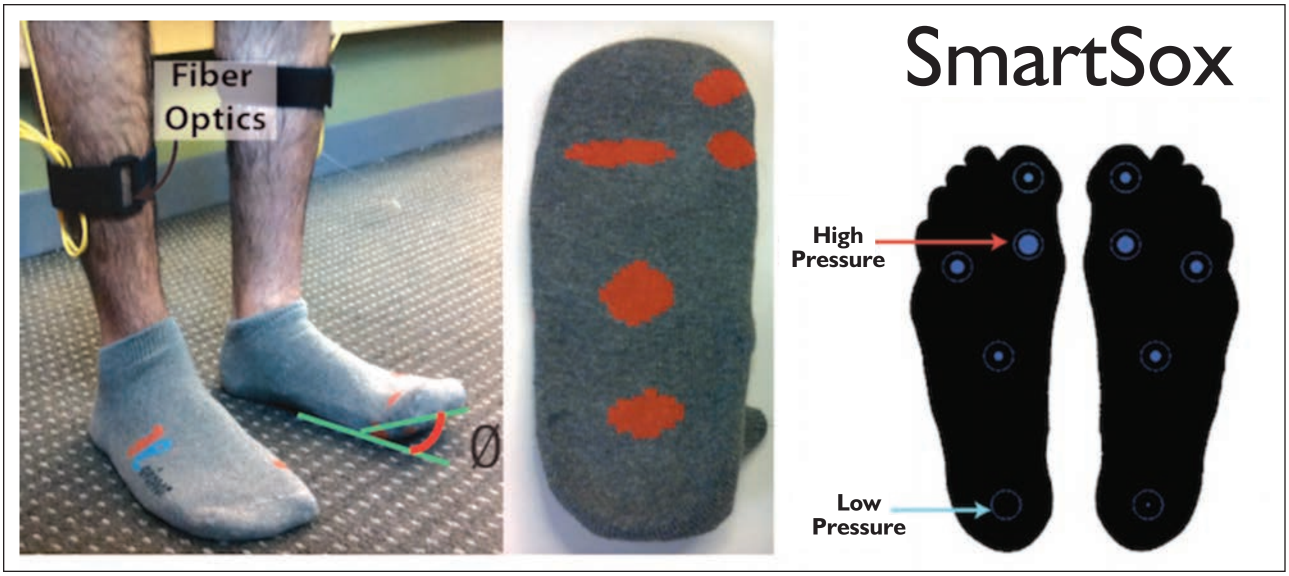

Figure 4: Multiple sensors are integrated within the length of the sock. B. Najafi, 2017(24)

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only temperature but also pressure to the lower extremity (Figure 4).[24,25]

These sensors are not just limited to textiles but have also been embedded into a foot mat for routine and ease of use. The temperature of plantar surfaces can be measured by a telemedicine foot mat, which allows patients to routinely check their feet for any asymmetrical temperature differences.[26] Patients with asymmetric temperature differences can be at risk for developing ulcerations. Research has shown that a difference of 2.5C is able to detect 97% of diabetic foot ulcers before they present clinically.[26]

This new device is water-resistant, easy to use, and requires no configuration to set up. It has been developed to encourage daily monitoring, especially for the high-risk diabetic patient. These individuals are encouraged to check their feet daily; however, some may be non-compliant and others many underestimate subtle changes in their feet upon examination. These technologies are designed to engage patients with the hope of improving compliance by getting patients actively involved in their care (Figure 5).

Patients with asymmetric temperature differences can be at risk for developing ulcerations

Figure 5: The Podimetrics Mat™ a thermometric mat desired for easy in-home use to monitor asymmetric skin temperature, which correlates to foot disease. R. G Frykberg, 2017(25)

Advances in Wound Care Products

Fish Skin Grafts

Decellularized fish skin as a dermal matrix is currently being used to assist in healing of complex lower extremity ulcerations.[27,28] It may seem out of the ordinary; however, it is a safe and effective option. There are no concerns about transmission of disease when applying fish skin over human tissue.[27] Also, fish skin has high levels of bioactive lipid mediators, which recently have been shown to play a key role in wound healing. High concentrations of Omega3 polyunsaturated fatty acids, such as Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are harvested from North Atlantic codfish.[28] Omega3 polyunsaturated fatty acid provides anti-inflammatory and anti-microbial properties and structural support, and permits the ingrowth of extracellular matrix.[29,30] Fish skin grafts can be used in an outpatient setting involving weekly graft application until the wound closes.

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Hyaluronic Acid Based Grafts—Hyalomatrix

Research has shown hyaluronic acid plays an essential role in wound healing. Its function cannot be understated. It has a positive modulating effect on cell proliferation, angiogenesis stimulation, and fibroblast migration.[31-34] As we age the body's ability to produce Hyaluronic acid diminishes, thus rendering its multifactorial function in wound closure.[35] Biomedical engineering has made advances to propitiate its utilization in wound healing. Hyalomatrix is a biosynthetic, acellular regenerative matrix containing HYAFF, an esterified form of hyaluronic acid, which prevents its degradation, and thus continues to support wound healing for up to 14-21 days.[35,36] Hyalomatrix is intended for deep burns and full-thickness wounds.[37] The use of this regenerative matrix may help lead to a reduction in scar formation and a more cosmetically acceptable appearance due to its role in supporting wound health.

Figure 6: Medline Corius ART™

Surfactant Agents—PluroGel

PluroGel is a highly concentrated surfactant (surface acting agent)-based product designed to be used in all stages of wound healing. Its unique design is made up of micelles, and each micelle has a hydrophobic core and hydrophilic surface. This results in the surfactant property that is attributed to cleaning appliances.[38] PluroGel is designed to be a multi-functional product. The hydrophobic core can trap wound debris and in doing so provide a debridement process as the wound heals. It can also maintain microvascular blood flow to the wound bed.[39,40] Its surfactant-based structure has been found to be able to penetrate biofilm, exposing pathogens to the body's own immune cells, thus allowing wounds to progress through the different phases of wound healing.[41,42]

Research also indicates that PluroGel can "plug" itself in areas of cell-membrane breakdown, preventing intracellular material from leaking into the wound bed while allowing these cells to repair themselves and preventing apoptosis.[43-45] It can be used in burn victims or routine wound care in any clinical setting.

Molecular therapy shows promise in the area of limb salvage.

What's to Come?

Regenerative Medicine—Gene Therapy

Currently, therapeutic goals for critical limb ischemia aim to re-establish blood supply, relieve pain, heal ischemic wounds, and prevent further amputations. For diabetic peripheral neuropathic pain, options include analgesic medications and lifestyle modifications to prevent progression of the disease, and/or management of its symptoms. The goal of regenerative medicine is to halt, or even reverse, the progression of diseases. Molecular therapy shows promise in the area of limb salvage. VM202 is a plasmid DNA containing two forms of Hepatocyte Growth Factor (HGF).[46] HGF is a potent angiogenic, anti-apoptotic, and neurogenic agent.[47,48]

Animal studies have shown that gene therapy can improve neuropathic pain as well as induce new blood vessel growth to improve blood flow in areas of ischemia.[49,50] This product is delivered intramuscularly to the affected limb, and preliminary studies have shown improvement in tissue oxygenation and reduction in neuropathic pain with its use.[51-53] HGF's ability to induce angiogenic and neurotropic properties make it an ideal agent to treat neuropathic and ischemic pain. Patients with critical limb ischemia, who are poor candidates for surgical revascularization, may also benefit from gene therapy. Research for this technology is still ongoing; however, the results are promising in the field of regenerative medicine.

Autologous Regeneration of Tissue

There also have been significant advancements in medical technology that aim to provide tissue coverage for ulcerations in the outpatient setting. The ART™ (Autologous Regeneration of Tissue) Skin Harvesting System (Figure 6) is a novel device manufactured by Medline Corius (www.medlinecorius.com). It is designed to harvest and transfer full-thickness autologous skin grafts.[54] The donor site is first prepped with local anesthesia using aseptic technique; the ART™ System then harvests microcolumns of full-thickness tissue—each microcolumn containing the full epidermis, full dermis, and a small tail of subcutaneous tissue. The device subsequently scatters the autologous tissue microcolumns into the recipient (wound) site.

Conventional skin grafting can lead to pain, infection, scarring, and possibly immobility. With the ART™ System, there is potential to negate these complications and provide a more effective skin-graft delivery system. Multiple

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clinical trials are currently underway with the ART™ System, but there are early indicators that it has the potential to provide easy management of chronic, tough-to-heal wounds with fewer complications in the outpatient clinical setting.

Conclusion

Diabetes and PVD continue to be a growing epidemic in our society, which has placed an enormous economic toll on our country. With new medical technologies, there is the potential to diagnosis these medical conditions before their detrimental complications arise. With hyper-spectral imaging, perfusion status to any tissue of interest can be seen, which increases the possibility of taking preventative measures before ulcerations arise. The utilization of smart socks and mats allows patients to be proactive in their health choices. And for complicated wounds, we are able to take a multi-directional role in protecting and healing them. All of these technologies allow us to establish a new standard of care in preventative medicine in the area of diabetic foot management. **PM**

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