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Review Article

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Wound Healing in Peripheral Arterial Disease:Current and Future Therapy

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Introduction

Peripheral vascular disease (PVD) is the third leading cause of cardiovascular morbidity with a global burden of over 200 million affected individuals [1]. Despite prevalent myth that this disease is confined solely to high income countries it is rather a disease process with worldwide impact [2]. As the incidence of diabetes mellitus, smoking, and increasing age rise globaly there will continue to be an increase in the incidence of PVD [2,3].

The economic burden is significant.In the United States alone, PVD accounts for over $20 billion in annual healthcare related costs [4]. Non-healing wounds represent a significant portion of this expenditure with the total cost estimate at more than $3 billion per year [5]. Wound care and wound prevention account for much of this direct cost. More difficult to measure are the indirect costs to the individual and society. This economic burden is only likely to increase in the next twenty years. Population studies project that the percentage of individuals over the age of 65 will double in the United States [6]. Escalating the problem further is the projection that the percentage of diabetes in that population will also increase [7]. Both age and diabetes are known dominant risk factors not only for the development of PVD but also that of PVD related tissue loss and wounds.

While PVD encompasses both arterial and venous disease processes, this review focuses specifically on the wounds associated with peripheral arterial disease (PAD). Arterial disease leading to tissue loss and chronic ulceration is estimated to affect 100,000 individuals in the United States annually [8]. PAD is often asymptomatic but its most common presentation is intermittent claudication, pain in the muscle of the leg with ambulation that is quickly relieved with rest [9]. Claudication rarely progresses to lower extremity wounds and therefore does not require urgent in line flow restoration [10].

A more significant degree of PAD is characterized by critical limb ischemia (CLI). CLI encompasses rest pain, continuous lower extremity pain most commonly in the feet secondary to severe PAD and tissue loss.The tissue loss is a progression from the rest pain and results in skin ulceration and gangrene, the source of PAD-induced wounds [3,9]. The incidence of CLI is 500 to 1000 new cases per million patients in Western society [3]. These patients carry high rates of limb loss and death within the next year so aggressive care of their disease and wounds is imperative and requires urgent arterial in flow restoration to heal lower extremity wounds [3,9].

This paper reviews the pathophysiology of PAD and its association with wound development. We summarize the current therapy available to improve PAD-induce wounds and present the active research in this field that may lead to new treatments. Finally, we review how the use of a team-based approach is necessary for treatment and provide the best outcomes for the patients.

Pathophysiology

Normal wound healing consists of regulated and integrated phases: hemostasis, inflammation, proliferation and tissue remodelling [11]. Oxygen plays a central role in each step of the healing process. PAD interrupts this normal process by creating a system of localized hypoxia. Despite their limitations, mathematical models have demonstrated the importance of oxygen for normal physiologic wound healing [12]. Initially hypoxia initiates the inflammatory step of wound healing by boosting reactive oxygen species activity, which in turn further activates platelets and induces cytokine release [13]. Chronic, however can impair proliferation by decreasing neo-angiogenesis [14]. Further tissue remodeling is dramatically affected by the concentration of oxygen. In this phase, we see the differentiation of fibroblasts to contractile myofibroblasts triggered specifically by oxygen and mediated by Transforming Growth Factor- β1 (TGF-β1), Transforming Growth Factor- β2 (TGF-β2), and Platelet Derived Growth Factor (PDGF) [15,16]. As healing progresses the initial type III collagen is replaced by the more permanent type I collagen, which is mediated in an oxygen dependent fashion by fibroblasts [16,17] (Figure 1).

PAD has its effects on the local wound environment by macrovascular and microvascular processes. Macrovascular disease is the sequelae of atherosclerosis on larger axial vessels. The earliest vascular change here begins with intimal thickening which consists of increased smooth muscle cells and abnormal deposits of extracellular matrix within the tissue [18]. Initially, blood flow is minimally affected but as the disease progresses there is increased disruption of flow and consequently the creation of an ischemic environment [19]. Unlike ulceration from venous insufficiency, where disease usually arises in the distal leg or so called "gaiter" regions, arterial leg wounds typically affect the forefoot or toes, though wounds presentat any spot distal to the arterial perfusion abnormality may suffer from non-healing regardless of original etiology.

A compounding factor common in PAD patients is the effect of compromised mobility on their disease process [20]. Diminished mobility can lead to prolonged periods of unrelieved pressure on the extremities resulting in increased shearing force applied to the skin and underlying tissues leading to a decrease in oxygen tension and eventual tissue necrosis.

Chronic wounds have several key phenotypic differences as compared to acute wounds. They have a lower concentration of growth factor receptors as well as lower mitogenic potential, which prevents normal response to physiologic stimuli.Fibroblasts isolated from patients with PVD and diabetes have abnormal responses to Insulin Growth Factor (IGF), Platelet Derived Growth Factors – A&B (PDGF-A,B),and Basic Fibroblast Growth Factor (bFGF) applied either in combination or alone [21-23]. Fibroblasts in the ischemic tissues of PAD have decreased mobility resulting in poor granulation of the wound bed [24].

The underlying molecular and cellular pathways in PAD are complex and to date not fully understood, but great strides have been made in diabetes mellitus-induced PAD. Diabetes mellitus acts synergistically to accelerate PAD. Diabetes through the effect of hyperglycemia on the acceleration of atherosclerosis increases this process while also preferentially targeting distal vascular beds [24,25]. Endothelial dysfunction and progression of both micro and macro vascular disease in the diabetic population seems to be mediated by decrease in nitric oxide (NO) bioavailability. Hyperglycemia blocks the activity of endothelial NO synthase and thereby increases the number of reactive oxygen species causing damage at a microvascular level [26]. Insulin resistance at the cellular level leads to increased free fatty acids, which can cause further oxidative damage and activation of proinflammatory pathways such as the mitogen-activated protein kinase pathway [27]. The effects of diabetes mellitus appear to be very early in the disease process with the rates of PAD being similar between pre-diabetic and diabetic patients [28]. Genetics is also important with patient with relatives with PAD have a two-fold increase in PAD regardless of other disease conditions [29]. While many aspects of vascular and wound physiology are yet to be fully understood, current therapy seeks to increase perfusion and decreased localized hypoxemia to heal ischemia-induced wounds.While there is still considerable work to understand the molecular basis for PAD and its progression to tissue gangrene and wounds, the pathways currently understood serve as the basis for the current translational research.This work exemplifies the need for our current treatment strategies to reduce risk factors and restore perfusion as well as the need for newer therapeutic modalities.

Current Standards in Therapy

Arterial disease-induced lower extremity wounds have inadequate perfusion therefore restoring arterial inflow to the extremity is the primary goal of all current therapy [30]. There are three major avenues to improve vascular perfusion: medical management, open surgery, and endovascular surgery.

Medical management

Patients with PAD also have a high rate of coronary arterial disease (28-94%) and increased risk of stroke (twice non-PAD patients) [31,32]. Therefore lifestyle modification and medical management of peripheral arterial disease and the associated risk factors such as smoking, diabetes mellitus, hyperlipidemia, hypertension, and hypercoagulability, are indicated for all patients with PAD. Smoking cessation is vital for patients with peripheral vascular disease as the association between smoking and development of PAD is greater than with coronary artery disease.Active smokers have an odds ratio for PAD of 2.67 compared to non-smokers that decreases to 1.67 in former smokers.While the risk of PAD does not go to non-smoker levels it does decrease and therefore aggressive smoking cessation is required [33,34]. Supervised exercise programs improved walking distances in claudicants with PAD [34-36]. Hyperlipidemia control with statins has been demonstrated to improve limb salvage rate in critical limb ischemia [37,38]. Strict glucose management after intervention is also associated with improved limb preservation [39]. Anti-platelet agents have not been individually demonstrated to improve limb salvage, however, aspirin has been shown to marginally improve limb survival after bypass surgery [40]. When patients with peripheral arterial disease stop smoking, and adhere to a statin, aspirin, and angiotensin converting enzyme inhibitor therapy there is a significant improvement in major limb adverse events [41]. Medical management of PAD involves significant lifestyle modifications, but when implemented there can be drastic improvements in PAD symptoms as well as progression of the disease [34].

Cilostazol, a phosphodiesterase-3 inhibitor, is frequently used in patients with claudication for its vasodilatory and anti-platelet actions.Cilostazol has also been shown to improve skin perfusion pressure in severely ischemic limbs [42]. The use of cilostazol, after angioplastyon critically ischemic limbs, has also demonstrated improvement in amputation-free survival, reduced restenosis, and reduced re-intervention rate [43-45]. Recently a small clinical trial has demonstrated the potential for improvement in ischemia-induced wounds with the combination of clopidogrel and cilostazol in patients who are not candidates for any intervention to improve perfusion [46].

Surgical therapy

While advances have been made in the medical management of lower extremity ischemia-induced wounds, large arterial revascularization remains the current standard of care.Open bypass surgery is often employed to bypass stenotic arteries and improve perfusion to lower extremity wounds with one-year patency reported to be over 80% for more proximal bypasses [30,47]. Distal landing zones for bypasses often are the popliteal, tibial, and peroneal arteries. However, when required, bypass grafts onto the pedal vessels have been shown to be feasible with 67% of the patients being able to still ambulate at three years [48]. Autologous vein is the optimal material for lower extremity bypass grafts [49]. Specifically the greater saphenous vein is the conduit of choice, but if not available arm or short saphenous vein may be used with foot preservation rates of 75% at 5 years [50]. When autologous vein is not available other alternatives include sythetic materials such as Dacron, polyterafluoroethylene (PTFE), cryo-preserved allograft veins, and deep calf vein arterialization with less degrees of patency [51-55]. Historically, the healthiest available tibial artery has been used as a target for bypass in critical limb ischemia, but current research is demonstrating that use of the angiosome model, which involves bypass to the specific tibial artery that is known to distribute blood to the specific wound location may be a more effective strategy [55,56].

Endovascular surgery

Over the last two decades, endovascular intervention has emerged as an additional therapy to improve perfusion to ischemia-induced wounds.This therapy has grown exponentially as it is minimally invasive, may have lower associated morbidity and mortality, and is practiced across multiple specialties. It is associated with lower primary patency than surgical revascularization, but may have comparable limb salvage rates [30,57]. The technical aspects and success of this therapy is constantly changing as new technology continues to emerge.It has been shown to be successful in limb preservation even with below-the-knee procedures and newer technology to address even small tibial vessels with endovascular therapy continues to evolve [58-60].

The diabetic PAD patient is classically been difficult to treat with high rates of death and major amputations, but recently endovascular therapy has emerged as effective treatment for diabetic ulcers [61- 63]. Rates of diabetic ulcer healing have neared 60% with complete healing near 45% after lower extremity endovascular therapy [63]. In this population, the presence of obesity was associated with poor outcomes from the procedure [62]. Elevated C-reactive protein and being currently on hemodialysis were associated with non-healing or reoccurrence of the ulcers [62,63]. While still not perfect, endovascular therapy is showing promise in diabetic PAD patients.

Efficacy and safety of endovascular therapy and open surgery are often compared [30]. Many trials have established the limb salvage rate of both open surgery and endovascular to be similar with one year limb salvage rates around 88% [49,64]. Mortality and amputation rate are similar between both modalities, but major adverse limb events were seen following endovascular procedures [49]. In specific populations, such as the extremely elderly or in those with significant comorbidities, endovascular therapy has been shown to be superior largely due to its lower peri-operative mortality and morbidity [65,66]. With good data to support the use of both open and endovascular therapy one therapy cannot be deemed superior to the other. Many factors such as anatomy, patient condition, prior surgeries, as well as the practitioners' comfort level should be used in selecting the modality of therapy to utilize [49].

Local wound care

In addition to improved perfusion of lower extremity wounds, local wound care is required to expedite the healing process and prevent infection.Several treatments are implemented for wound care and include mechanical debridement, enzymatic debridement, tissue protection, and hyperbaric oxygen therapy [30,67]. While many methods and therapies are employed for debridement and protection most are without supporting evidence-based research [68]. While the data is sparse there are several trials looking at topical treatment of wounds (Table 1). Hyperbaric oxygen therapy is becoming increasingly used for the local care of non-healing wounds.In diabetics with critical limb ischemia, hyperbaric oxygen may promote wound healing, but overall one year amputation-free survival rate remains unchanged demonstrating that this therapy may help the wound but not the source of the problem [45,67].

Amputation

Ultimately, if local wound care and restoration of arterial perfusion fails to heal lower extremity wounds, amputation becomes necessary.There are multiple factors that contribute to critical wound ischemia progressing to amputation. These include diabetes mellitus, hypertension, renal insufficiency, elevated body mass index, active smoking, age, and hyperlipidemia [64,69]. Unfortunately, only 48- 75% of those who progress to amputation had prior re-vascularization attempts one year before amputation [30,69]. Therefore we are not maximizing our current therapeutic options.All reasonable attempts to preserve these limbs should be made as once a patient has at least one below knee amputation they are more likely to have a contralateral amputation and an earlier mortality [69].

There is significant cost to the care of peripheral arterial-induced lower extremity wounds.The amount of resources and money has been challenged in the literature [70], but recent research has demonstrated that aggressive revascularization may lead to healthcare cost savings compared to local wound care and even amputation [71]. These cost savings were even noted in high-risk individuals with end stage renal disease. In these patients, there was significant cost savings (although marginal health improvement) in those who underwent revascularization compared to amputation and wound care alone [72].

The standard of care for patients with lower extremity wounds secondary to ischemia should be revascularization with local wound care as an adjunct but not monotherapy whenever possible. However we are not reaching every patient who could benefit from revascularization. In addition the current standards in treatment are limited and do not entirely improve distal wounds or prevent amputation. Therefore novel techniques that can improve the overall outcomes and potentially reduce cost are necessary. For this reason the current research being conducted on PAD is vital to improve the treatment of PAD-induced wounds.

Current Research

While new technology may lead to slight improvements in outcomes, the greatest improvements in arterial-induced wound care may come from the bench.Current translational research for the treatment of peripheral arterial disease and subsequent lower extremity wounds focuses on improving perfusion through therapeutic angiogenesis. These areas include gene therapy for angiogenesis, stem cell induction of angiogenesis, and microRNA regulation of angiogenesis.

Gene therapy

Gene therapy in vascular disease uses recombinant protein or genes for angiogenic growth factors that are used with the intent of increasing collateral circulation and enhanced perfusion to the ischemic tissues of arterial diseased-induced wounds [73]. Clinical trials have attempted multiple forms of delivery including viruses, plasmids and both intra-arterial and intra-muscular injections [74]. The greatest success in delivery of pro-angiogenic genes to ischemic tissue has been with adenovirus-based vectors, but due to the ease of administration intramuscular injections of vectors is the most commonly used in clinical trials [73,75]. The pro-angiogenic factors that have been studied as potential targets include: vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hypoxia-inducible factor 1 (HIF-1), hepatocyte growth factor (HGF), and developmentally regulated endothelial cell locus-1 (Del-1) [73-79]. All have been shown to have efficacy in pre-clinical rodent models and been shown to be safe in phase I trials, but have had mixed results in phase II efficacy trials [75- 77].

The most widely studied gene to date has been VEGF, which is known to regulate vascular growth, increase vascular permeability, and mediates angiogenesis [77]. VEGF gene therapy with both plasmid and viral vectors has been shown to increase collaterals and tissue perfusion in rodent models [78,79]. Results of these trials have demonstrated improvement in collateral circulation and subjective improvement, but they have failed to show objective results in healing ulcers, preventing amputations, improving walking time, improving claudication, or increasing ankle-brachial indexes (ABIs) [74,78]. Several PAD clinical trials reported increased lower extremity edema after VEGF gene therapy treatment [74,78,79]. Of the three phase II clinical trials conducted, only one showed positive results with increased vascularity, which has been questioned to be a reliable endpoint [73].

The only phase III clinical trial of gene therapy conducted for PAD has been with FGF-1, which modulates proliferation and migration of several cell types vital for angiogenesis [77]. This study was conducted after a phase II trial had shown promise for improved ulcer healing and reduced amputation rate by four serial doses of intra-muscular injections of FGF-1 plasmid [75,77]. The phase III trial failed to demonstrate any efficacy in amputation rate or ulcer healing and hence this has not been approved for routine use [75,77].

While pre-clinical research has shown promise in gene therapy for improving perfusion in critical limb ischemia, the clinical trial data is mixed at best.Hammer et al. conducted a meta-analysis on 12 randomized-controlled clinical trials of gene therapy for PAD and concluded that gene therapy was safe and well tolerated. When they evaluated the efficacy of gene therapy they concluded there was no significant improvement in all-cause mortality, amputation rate, and ulcer healing with the use of gene therapy compared to controls [76]. Certainly further research both in the lab and in the form of clinical trials is required before this therapeutic approach can be used routinely.

Cell-based therapy

Cell-based therapy involves the introduction of progenitor cells that have the potential to initiate vasculogensis or post-natal angiogenesis, which is the development of new vessels from endothelial progenitor cells that differentiate and mature into new vessels [77]. These endothelial progenitor cells are thought to release pro-angiogenic factors that mediate a paracrine effect on the surrounding local environment [74]. Cells that are being evaluated for potential therapy include endothelial progenitor cells (EPCs), bone marrow mononuclear cells (BM-MNCs), mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), human embryonic stem cells from cord blood (hESCs), and induced pluripotent stem cells (iPSCs) [74,77,80-85]. In addition to specific cell transplantation, stem cell-stimulating cytokines such as granulcyte macrophage-colony-stimulating factor (GM-CSF) are employed to upregulate existing stem cells in ischemic tissues [77].

EPCs are derived from the peripheral blood and can be found within tissues as well [83]. EPCs are involved in the creation of new capillaries and secretion of cytokines that induces other endothelial cells to proliferate with in the ischemic tissue [77,83]. In most critically ill patients such as those with critical limb ischemia, circulating progenitor cells are rare. Therefore, EPCs are derived from stimulated (with GM-CSF) bone marrow or ex vivo expansion of EPCs of circulating progenitor cells with differing degrees of selection based on their cellsurface antigens [77,82]. Studies of GM-CSF as a monotherapy in PAD to increase circulating EPCs for critical limb ischemia have failed to show significant clinical improvement in patients. However one trial showed improved walking time [82]. Early trials of GM-CSF of efficacy have shown improvement in exercise capacity, ulcer healing, ABIs, toe brachial pressure index, and tissue oxygenation [74,77,83].

BM-MNCs are derived from bone marrow aspirates that are centrifuged to obtain several types of multipotency stem cells that serve as hematopoietic stem cells [77]. Animal trials demonstrated increased neovascularization in ischemic limbs which lead to clinical trials [77]. Clinical trials on CLI demonstrated the injection of BM-MNCs to be safe in comparison to controls and improvement in ulcer healing, amputation-free surivial, rest pain, ABIs, and tissue oxygen pressure [74,77,82]. Administration of the BM-MNCs has mostly been intramuscular, but one trial with intra-arterial injection did demonstrate improved wound healing and demonstrated improved efficacy after repeated doses [74,82]. BM-MNCs when compared to non-mobilized peripheral MNC demonstrated improvedABIs and rest pain showing a greater EPC fraction available from the bone marrow [82].

MSCs are derived from bone marrow as well, but are not hematopoetic in nature [77,85]. These cells have created great interest because of their ease of isolation, lack of immunogenicity, ease of modification with specific genes, ablility to expand ex vivo, and safety of systemic or local delivery [74,77,80,81]. The mechanism of action for these cells is strictly through release of cytokines that induce endothelial cells to proliferate and differentiate into new vessels [77,85]. Therefore many of the clinical trials thus far have used these cells in combination with other cell lines such as EPC and BM-MNCs. In combination with BM-MNCs, MSCs have shown improvements in rest pain, exercise tolerance, ABIs, tissue oxygen pressure, and collateralization [77]. In a head-to-head comparison of BM-MNC and MSCs the rate of diabetic foot ulcers in CLI was noted to be faster as well as improved tissue oxygenation and improved walking distance with MSCs[74]. Allogeneic MSCs derived from healthy donors injected intramuscularly in to ischemic lower extremities have been demonstrated to be safe and trended toward improved ABIs [81]. Allogeneic umbilical cord blood MSCs have also recently studied to be safe for patients with CLI [80]. Cell therapy holds great promise for future treatment of lower extremity wounds secondary to PAD.

The work in cell therapy has occurred concomitant with the progress in gene therapy.One could surmise that there may be an increased effectiveness by combining these two therapies.While this has not reached human trials, work in animals has shown promise in improved perfusion in in PAD with the combined gene and cell therapies of HGF and BM-MSCs, respectively improving perfusion in ischemic rodent limbs [86]. While still removed from human trials these early advances show promise to overcome the current disappointing results of the current monotherapy trials.

mIcroRNA therapy

microRNA (miRNA) therapy is one of the newest areas of research in treating critical limb ischemia with tissue loss.While these noncoding pieces of RNA were only discovered a little over two decades ago they have been found to have significant roles in many biological functions including angiogenesis and wound healing [87]. miRNAs are found virtually in all tissues and bind to specific post-transcriptional mRNA causing gene silencing through inhibition of translation and eventual degradation of the mRNA [88]. Each miRNA has multiple mRNA which it binds to and alters their translation in addition the expression of mRNA is different between tissues and states of tissues [87-89]. When tissues are in a hypoxic state a subset of miRNAs are induced or increased in expression that are known as hypoxamiRs [88].

HypoxamiRs are up-regulated in ischemic tissues.A portion of hypoxamiRs may be in fact known to be inhibitory to tissue repair, but another subpopulation appears to promote tissue repair and some angiogenesis and hence have been termed angiomiRs [90]. Current research is establishing whether each altered miRNA is beneficial or detrimental to wound healing.HypoximRs appear to be involved with regulation of inflammation, control of redox reaction, angiogenesis, and tissue repair [87,91]. The presence of hypoxamiRs appears to alter the response of certain cells, specifically endothelial cells to ischemia specifically by allowing the production of reactive oxygen species to promote angiogenesis [92]. Some miRNA that are down-regulated during ischemia appear in normal tissue to inhibit angiogenesis and other forms of tissue repair, but during hypoxia are lost and allow cellular regeneration machinery to function in repair of the cell such as VEGF, hypoxia-inducible factor (HIF) and metalloproteinase-9 (MMP- 9) [91,93]. Two specific miRNAs that have been identified in hypoxic tissues are miR-21 and miR-210.The presence of both of these miRNA within the wound hinders the wound's healing.Stragies to downregulate both of these miRNA may aid in wound healing [88]. While still in pre-clinical research hypoxamiRs are interesting potential therapies for ischemia-induced wounds in that the molecule is relatively stable for delivery and has the potential to effect multiple gene expressions resulting in an amplification of action [87]. HypoximR therapy may even be used to alter bone marrow vascular stem-cell populations to allow for up regulation and better utilization of these cells in patient predisposed to ischemic wounds such as diabetic patients [94].

AngiomiRs are a subpopulation of beneficial hypoxamiRs that appear to promote angiogenesis and are of great interest for the treatment of ischemia-induced wounds [90,93]. These miRNA appear to regulate key genes in angiogenesis such as VEGF, Ephrin-A3, IGF- 1, Thrombospondin-1 (TSP-1) and others [95]. AngiomiRs appear to regulate several aspects of angiogenesis including proliferation, migration, and morphogenesis of endothelial cells [90]. In fact, progenitor bone marrow cells, which are known to induce angiogenesis in hypoxic tissue, have been shown to express and even secret angiomiRs [96]. miR-126 is a specific angiomiR with therapeutic potential as it is specific to endothelial cells and has been shown to promote vascular integrity and induce angiogenesis [90]. The introduction of miRmimics or miR-vectors containing miR-126 into ischemic wounds have the potential to promote microvascular production and wound healing. The potential to target multiple aspects of angiogenesis makes angiomiRs intriguing new therapeutics, but their use will have to be carefully evaluated as they have the potential to induce angiogenesis in un-idenified tumors and the side-effects of the miRNA inhibitors and mimics systemically is unknown [89,90,95].

Active clinical trials

A majority of active clinical trials in PAD-induced wound treatment are expanding upon the evolving translational research. The active clinical trials are focusing on the use of autogenous stem cells for neovascularization of limbs with critical ischemia.The source of stem cells ranges from bone marrow pluripontent stem cells to circulating monocytes and tissue-specific multipotent stem cells [97].

Medical therapies currently under investigation include reevaluation of the classic anti-platelet drugs such as aspirin and clopidogrel as well as several more non-conventional medications such as iloprost and urokinase.One study has theorized that high hematocrits create increased blood viscosity which hinders perfusion in ischemic limbs with existing wounds therefore patients are being enrolled for controlled phlebotomies to aid in lower extremity wound healing [97].

Trials for endovascular therapy are evaluating the use of new technology including laser-atherectomy devices, drug eluting stents for below knee interventions and the use of drug-coated angioplasty balloons. Open surgical clinical trials are less prevalent as the techniques are more mature, but there are ongoing evaluations of the patency of a variety of vascular grafts.Two trials are comparing the efficacy of endovascular intervention versus open surgery for restoring perfusing to critically ischemic limbs. One is evaluating approaches based upon clinical effectiveness while the other is look at this from cost-savings perspective [97].

This research may lead to exciting new therapeutic modalities for the treatment of PAD-induced wounds in the future.As these new discoveries and technologies are added to our current armamentarium multiple specialists will be required for the most effective utilization. Hence, the need to for PAD wound team.

Team-Centered Therapy

With the complexity of available therapies the treatment of non-healing chronic wounds attributed to PAD requires complex surveillance, evaluation, and treatment from a broad spectrum of healthcare practitioners. It has been recognized since the 1980s that a 'team' approach to this subset of patients with vascular wounds can provide improved care [98]. Further, having a diversity of expert opinion involved in each patient's care can help offset the challenges posed by the multitude of therapeutic options. This becomes critical given the widespread recognition ofneed to 'save life and limb'while having a lack of consensus and scarce evidence in the literature regarding the superiority of one method over another [99].

This challenge has led to the creation of comprehensive and systems based approaches to PAD related wounds. This team approach requires not only dedicated and specialized personnel, but also a financial commitment on the part of the health system [100]. While financial considerationsare important, first and foremost a commitment to a limb salvage program by a cross section of medical practitioners is requisite. At this time a multidisciplinary focus is critical as there is no single health care specialty which adequately houses the expertise and experience to provide comprehensive care for these varied wounds. When multiple specialties are invested in the creation of a dedicated wound care center there can be a greater than 50% reduction in amputation rates and subsequent wound related mortality [100-105]. The diversity and complexity of the health care team is reflected in the breadth of confounding variables in PAD related wounds including medical comorbidities, mobility limitations, and incompletely understood molecular pathways, and multiple often non-vascular etiologies of wounds.

The team must have a leader: a physician or surgeon who has a passionate focus on the development of a wound center and program. Critical team members can then be drafted to attain appropriate expertise. Many models have focused on the combined efforts of specialists in vascular and podiatric surgery [106]. These specialists combine knowledge of revascularization as well as lower extremity physical mechanics in the goal of limb salvage. While the medical and surgical expertise of these specialists is necessary, it is not adequate in the provision of wound care. Dedicated and specialized nursing staff who can help stream line the time intensive process of both in-patient and out-patient wound care and allow for successful transition between these two patient care realms are important. The role of social workers in wound care is often underestimated. Patients who suffer from PAD related wounds are many times found within a low socioeconomic class [107]. Patients with PAD related wounds will not have the optimal chance of success without the appropriate access to resources such as transportation and dressing supplies.

This expertise and dedication to patient care is associated with significant costs. At present the largest portion of direct costs is facility related fees which make up roughly 30% of annual expenditures [108]. With the present uncertainty regarding health care reimbursements and shifting compensation in Medicare and Medicaid the establishment of a wound care center does not guarantee a robust financial outcome. Indeed, most outpatient wound centers collect less than 40% of billable charges [108]. However, health care system revenue is offset by referrals to specialists as well as downstream revenue.The economics of individual health care systems are obviously a local concern. However, from aglobal standpoint,studies examining the economics of amputation have demonstrated that a reduction in amputation rates yields reduced total costs to the healthcare system as well as improved quality of life metrics for our patients [109,110].

Conclusion

Peripheral arterial disease is increasing in prevalence world-wide and subsequently ischemia-induced wounds are increasing as well. Currently, management of risk factors and restoration of blood flow to the ischemic limb are the standards of care.While work continues to improve our current surgical therapies some of the most exciting research is to promote angiogenesis in ischemic tissues through cell, gene and miRNA therapies. To help administer the new therapies as they become available and to give the optimal outcomes for these patients a multi-specialty team focused on ischemic limb wounds must be utilized.

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