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Limb Salvage for Diabetic Patients with Peripheral Arterial Disease

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LIMB SALVAGE FOR DIABETIC PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

by

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Abstract

Diabetes is rapidly increasing throughout the United States. According to the Center for Disease Control (CDC) (2017), the total number of patients diagnosed with diabetes is 23.1 million, patients with undiagnosed diabetes are 7.2 million, for a combined total number of patients with diabetes exceeding 30.2 million and growing. According to the CDC (2016), approximately 8.5 million people in the United States have peripheral artery disease (PAD), which includes 12-20% of individuals who are older than age 60.

According to a study performed by Swaminathan et al. (2014), 186,000 patients underwent lower extremity amputation (LEA). Data also shows that patients undergoing LEA have a mortality rate of 20% noted within one year, and a 40% to 50% mortality rate indicated within 18 months.

The review of literature analyzed studies that compared vascularization procedures to determine whether early diagnosis and intervention provide benefit to reduce lower extremity amputation in diabetic patients with peripheral arterial disease (PAD) and critical limb ischemia (CLI). The analysis of research also provides scientific data of which providers are performing revascularization procedures, what methods are being used to deliver these treatments, data about their success rates and their cost effectiveness.

After an extensive review of research, it was concluded that early detection and revascularization reduces LEA and increases the quality of life for diabetic patients with PAD and LLI (lower limb ischemia). Research suggests that limb salvage is cost efficient, although unpredictable factors such as patient compliance may skew cost analysis. However, data collected does support that if patients are compliant and clinicians implement a multidisciplinary approach to allow early recognition and intervention, limb salvage is cost efficient.

Introduction

The diagnosed population with diabetes in the United States is steadily increasing. An estimated 30.3 million people of all ages, or 9.4% of the U.S. population, had diabetes in 2015 Center for Disease Control, (CDC), (2017). An estimated 1.5 million new cases of diabetes (6.7 per 1,000 persons) are among U.S. adults aged 18 years or older in 2015 (CDC, 2017). The increasing cases of diabetes are also increasing other risk factors such as chronic kidney disease (CKD), heart disease, stroke, myocardial infarction (MI), and vascular diseases such as coronary artery disease (CAD) and peripheral artery disease (PAD), all of which are significant risk factor for lower limb amputations.

Considering more than 30 million Americans are diagnosed with diabetes, and with an estimated 382 million people diagnosed worldwide, diabetes is a global epidemic and is projected to be the seventh leading cause of death by the year 2030, according to the World Health Organization (CDC 2016). With the increase in diabetes comes the rise in risk factors and related health issues. Evidence supports that LEAs reduce quality of life and decrease the lifespan of diabetic patients with PAD.

PAD is a chronic disease and considered a major indicator of cardiovascular ischemic events including vascular occlusion which may lead to limb amputations. Although PAD is significantly associated with increased risks of ischemic events, lack of diagnoses and appropriate treatment leads to an increased population with LEAs which could have been prevented. Research has shown that early recognition and treatment of PAD reduces the risk of limb amputation, minimizes the risk of long-term disability, and improves quality of life.

Diagnosis of PAD in patients with diabetes can be a complicated disease and therefore requires a multi-faceted treatment approach, involving aggressive risk-factor modification,

antiplatelet therapy, and revascularization procedures. The American Diabetes Association (2016) recently issued a consensus statement on the epidemiology, pathophysiology, diagnosis, and management of PAD in patients with diabetes. The consensus associated PAD with a significant increase in the risks of cardiovascular and cerebrovascular ischemic events, including myocardial infarction (MI) and stroke. Patients with diabetes and PAD are at higher risk of lower extremity amputation than those without diabetes (The American Diabetes Association 2016).

The purpose of this scholarly project is to research early endovascular therapy and limb salvage in diabetic patients with PAD and determine if the effects reduce limb amputation and are cost effective.

Statement of the Problem

The number of lower limb amputations in the diabetic population with PAD is increasing at an alarming rate. Limb amputation has been known to cause depression, decreased quality of life, increase patient mortality and increased healthcare costs. According to Sanguily (2015), studies have shown that patients who undergo limb amputation due to diabetes above or below the knee have a 40 to 50 percent death rate within 18 to 24 months. Options for limb prevention need further research so that patients can have access to a higher quality of healthcare, affordable healthcare, and ultimately a better quality of life.

Research Questions

Will Early Revascularization Interventional Therapy Prevent Limb Amputations in Diabetic Patients With PAD? For this research paper, I will discuss the most likely benefits from

vascular procedures to include age, gender, ethnicity, and risk factors. I will determine if early revascularization provides any benefit to prevent limb amputation, based on scholarly research.

What is The Key to Success to Prevent Limb Salvage in Diabetic Patients with PAD? For this research paper, I will discuss what makes early revascularization successful to include a multidisciplinary approach, which is the key to success for vascularization in diabetic patients with PAD.

Is Early Revascularization Interventional Therapy and Limb Salvage for Diabetic Patients with PAD Therapy Cost Effective? For this research paper, I reviewed multiple analyses of costs for patients to include therapy for diabetes, diabetes education, vascular treatment, and lower extremity amputation to conclude if early revascularization is cost effective.

Literature Review

The literature review yielded high quality studies concerning pathophysiology, etiology, epidemiology, risk factors, limb amputation, revascularization interventional therapy, and costs of care in patients with diabetes and PAD. To date, I have researched data to support early interventional revascularization therapy in those who are performing these procedures. I reviewed literature that may contradict early revascularization intervention or provide sufficient evidence to why it would not be beneficial. Although revascularization interventional therapy is a universal standard of care for patients with limb ischemia, early interventional treatment is not a standard of care. Therefore, finding large randomized controlled studies have been difficult. I have included studies using Access Medicine, CINAHL, Clinical Key, PubMed, Cochrane, ScienceDirect and Google Scholar. Key words used; PAD, peripheral arterial disease, limb

ischemia, non-traumatic limb ischemia, diabetic neuropathy, diabetic foot ulcers, revascularization procedures, and peripheral vascular disease.

Pathophysiology, Risk Factors, Etiology, and Epidemiology of PAD and Diabetes

Type 1 diabetes mellitus is due to an autoimmune reaction involving beta eta cell destruction, usually leading to insulin deficiency. Type 2 diabetes mellitus is generally due to a progressive loss of beta cell insulin secretion or insulin resistance. Gestational diabetes mellitus is diabetes diagnosed in the second or third trimester of pregnancy in which a patient had not previously been diagnosed with diabetes before gestation. Type 2 diabetes is a more common risk factor for PAD and limb ischemia, and for this research paper I will focus more on the pathophysiology of type 2 diabetes mellitus.

Type 2 diabetes mellitus is a heterogeneous disorder that affects various ethnic groups. According to the CDC (2017) Native Americans, Hispanic-Americans, and Asian-Americans are the most impacted populations of the United States. Type 2 diabetes mellitus is characterized by impaired regulation of hepatic glucose production, peripheral insulin resistance and declining beta cell function which leads to beta cell failure. Many organs are associated with type 2 diabetes mellitus and contribute to chronic hyperglycemia and insulin resistance. These include those that code for beta cell function which allows the body to detect rise and fall in blood glucose levels, and the ability to synthesize and secrete insulin, glucose, and glucagon. The combination of genetics and environmental influence are the essential components of pathophysiologic mechanisms of type 2 diabetes mellitus (McCance, 2014).

Insulin resistance is defined as a decreased response of insulin-sensitive tissues to insulin. These sensitive tissues include liver, muscle, and adipose. Many factors can contribute to the

disruption of insulin signaling pathways that contribute to insulin resistance. These include down-regulation of insulin receptors, high amounts of insulin antagonists, a decrease in activated post-receptor kinases and alteration of glucose transporter proteins. Risk factors associated with type 2 diabetes mellitus may include but are not limited to central obesity, metabolic syndrome, hypertension, dyslipidemia, atherosclerosis and diets high in sugars, carbohydrates and fats, especially alcohol.

Diabetes mellitus type 2 may be diagnosed based on criteria of a hemoglobin A1c (HbA1c) $\geq$ 6.5%, a fasting plasma glucose on two separate occasions $>$ 125 mg/dL, a two-hour glucose tolerance test results > 200 mg/dL, or a random plasma glucose level > 200 mg/dL plus symptoms of hyperglycemia. Fasting is defined as no caloric intake for at least 8 hours. The two-hour glucose tolerance test should be performed by using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water (Papadakis, 2017).

Peripheral artery disease (PAD), also known as a peripheral vascular disease (PVD), is a chronic condition in which the peripheral arteries or vessels typically in the lower limbs become occluded, restricting blood flow due to a buildup of calcium or fatty deposits (atherosclerosis). The most significant risk factors are diabetes and smoking which cause vessels to harden and become less pliable, and hypercholesteremia which increases risk for vessel occlusions, which begins to have an effect typically in the 5th decade of life. However, most people do not become symptomatic until age 60-65 years of age.

Symptoms of PAD do not usually appear until the artery has occluded by 60 percent or more. The first signs of intermittent claudication can include leg cramps typically in the calves that develop with activity and are relieved by rest usually within five minutes. Other symptoms may include the feeling of leg heaviness, weakness, numbness, tingling, foot wounds that do not

heal, changes in skin color, cold feet and burning sensation, especially in the feet or toes when lying flat at night.

PAD can be diagnosed through patient history, physical exam and various diagnostics and evaluations. Duplex ultrasound is the most widely used modality to assess location and degree of stenosis, as well as patency of bypass grafts with a sensitivity and specificity of stenosis from the iliac artery to the popliteal artery, are 90% and 95%. However, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) remain the gold standard for diagnosis (Papadakis, 2017).

Limb Amputations and Early Interventional Revascularization Therapy in Diabetic Patients

An online database search of PubMed and Cochrane review was conducted to provide scholarly articles related to diabetic patients with PAD, critical limb ischemia (CLI), and interventional revascularization, in cohesion with limb amputation. Over 170 million people worldwide have diabetes mellitus (DM), and the worldwide burden is projected to increase to 366 million people by 2030 according to CDC (2015). DM and smoking are considered among many to be the most significant risk factor of PAD which leads to critical limb amputation (CLI) and can be associated with end-stage PAD. Because PAD is ultimately caused by occlusion or atherosclerosis, revascularization is the most beneficial therapy to prevent limb amputation. A systematic review conducted by Thiruvoipati et al. (2015), concluded that within the Medicare population, more than 50% of patients with DM acquire CLI, and 23.5% require LEA at ages 65-74 with an ankle brachial index (ABI) less than 0.9. The atherosclerotic disease accounts for 44% of the mortality rate due to limb amputation in patients with PAD and CLI. Most patients

with CLI can be revascularized; however, the presence of gangrene can limit successful limb preservation. Therefore, in these cases, amputation may be the best option which is why early detection and intervention is a hallmark for preserving limbs.

Revascularization can be accomplished via open vascular surgery and endovascular therapy. Unfortunately, limited data is available to help identify protocols for revascularization strategy, including when intervention should be initiated. However, within this research paper, I will discuss a few studies regarding early revascularization. Dr. Julio Sanguily who specializes in vascular surgery at Martin Health Systems of Florida has had great success in reducing limb amputation by providing early revascularization procedures over the past ten years (Sanguily, 2016).

Arterial revascularization improves the prognosis of PAD and is considered by many to be the treatment of choice, even in diabetic patients who have higher risk factors and require a multidisciplinary approach to care to increase success rates. Florian (2007), conducted a meta-analysis to determine if early revascularization provided benefit in limb salvage. The study included a total of 416 patients with PAD, 190 which also had a history of DM. The study suggests that arterial revascularization, regardless of whether percutaneous transluminal angioplasty (PTA) or open surgery, was associated with a significantly higher sustained clinical success rate at one year, with a higher amputation-free survival rate as compared with conservative therapy alone. Delay of arterial revascularization was associated with poorer outcomes than immediate revascularization. This difference was statistically significant in nondiabetic patients and showed a strong trend in diabetic patients. Prompt revascularization, regardless of whether it was PTA or reconstructive surgery, was independently associated with favorable outcomes compared with delayed revascularization or no revascularization.

According to Florian (2007), recommendations call for attempts of arterial reconstruction in any patient with CLI if the one-year probability of survival and limb salvage is estimated at 25%. He also states that PTA, with or without stenting, is the first line approach for CLI because results are similar to reconstructive due to advantages of low infection rates and shorter hospital stays.

In conclusion, DM is associated with a much higher severity and diffuse PAD relative to nondiabetics, which correlates to a higher risk of mortality and impaired quality of life. Therefore, a multidisciplinary approach of different specialists to include primary care, cardiology, vascular surgery, internal medicine, podiatry, wound care specialists, nutritionist, and diabetes educators to coordinate care are needed to improve the clinical outcomes and quality of care in this patient population.

A retrospective cross-sectional study by Sadigursky and Badaro (2017), discusses complications of DM that cause amputation of the lower extremities. This study aims to assess risk factors and pathological complications that justify amputations. Data evaluated pathology reports and medical records of 245 patients over a period of five years which concluded that gangrene was the predominant cause of amputations, 40% of those were infrapatellar amputations of which 50% was more common in patients with vascular disease.

A meta-analysis performed by Tsujimura (2017) investigated two-year clinical outcomes after implantation of Epic Stents which is self-expanding nitinol stents for patients PAD due to the aortoiliac occlusive disease (AIOD). The study was conducted on 217 patients which underwent stent placement therapy. These patients exhibited a variety of underlying medical conditions to include diabetes, renal failure, and critical limb ischemia. Results of the study

concluded The Epic Stent was demonstrated to be safe and effective for AIOD when tested for two years in patients with PAD.

Interventional Vascular Therapy and Limb Salvage for Diabetic Patients with PAD

A systematic review was conducted by Abbasi (2002). The goals of the study were to define the relationship between body mass index (BMI) and insulin resistance in 314 nondiabetics, normotensive, healthy volunteers and determine the relationship between these two variables and coronary heart disease (CHD) risk factors. The results of the study conducted concluded that obesity and insulin resistance are both powerful predictors of CHD risks, and insulin resistance at any given degree of obesity accentuates the risk of CHD and type 2 diabetes.

Although this study alone provided limited evidence to conclude the degree that obesity and insulin resistance lead to coronary heart disease, based on one study, scientific based evidence does support its findings concluding that obesity and insulin resistance are major indicating factor to the progression of CHD.

A meta-analysis conducted by Swaminathan et al. (2014) analyzed data provided by U.S. Medicare from 2000 through 2008 to conclude that of the three million patients hospitalized with PAD, 186,338 (6.8%) received LEA. Patients who underwent LEA had mortality rates that were nearly twice as high as those who did not experience LEA at 30 days (13.5% versus vs. 6.9%), one year (48.3% vs. 24.2%), and three years (70.9% vs. 43.2%). This article supports the fact that limb salvage increases not only quality of life but decreases mortality.

The meta-analysis by Conte et al. (2015) discusses diagnoses and therapeutic guideline recommendations for diabetic patients with asymptomatic PAD and claudication. The meta study reviewed conducted 34 studies that examined the prevalence and risk factors of PAD. This study provides epidemiology and risk factors, diagnosis and recommendations of PAD, management of

asymptomatic patients with PAD, interventional and noninterventional management recommendations, as well as preventative guidelines.

A meta-analysis by Reekers et al. (2016) reviewed 56 studies of therapies used to revascularize diabetic and PAD patients with ulcerated feet from 1980 to June 2014. This article claims that PAD and infection are the primary causes of lower-leg amputation in persons with diabetes. According to Reekers et al. (2016) the major outcomes following endovascular or open bypass surgery were broadly similar among the studies (p 136). Following open surgery, 85% of patients-maintained limbs within one-year, and following endovascular revascularization, these rates were 78%. At one-year follow-up, 60% or more of ulcers had healed following revascularization with either open bypass surgery or endovascular techniques. Studies appear to show that limb salvage increased with revascularization procedures over conservative therapies. Therapies included in this study are wound healing, angioplasty first therapy, crural vessel angioplasty, pedal bypass graft, angiosome-directed therapy and limb salvage and amputation. Also discussed are infection, end-stage renal disease, early complications, perioperative mortality, and mortality.

Who is Who is performing early vascularization interventional therapy and limb salvage for diabetic patients with PAD?

New technology to include balloon angioplasty, medicated stents, and CSI are allowing cardiologist and vascular surgeons across the country to perform revascularization intervention to treat CLI and PAD. Patients whom presented with symptoms of claudication, neuropathy, and cold limbs are now offered minimally invasive procedures to prevent limb amputation. The key

to success in procedures such as these are early detection prevent irreversible nerve and tissue damage.

The American College of Cardiology/American Heart Association (ACC/AHA) created guidelines and recommendations using more than 1300 references using evidence-based methodologies to include prevention, diagnosis, treatment, and monitoring patients who present with claudication, CLI, and PAD Hirsch et al. (2006). Class one recommendations are conditions that provide evidence that procedures or treatment provides benefit and effectiveness. Class two recommendations conclude that there is conflicting evidence of efficacy of procedures or treatment. Level "A" evidence data is supported from multiple randomized clinical trials or meta-analyses. Level "B" evidence data is supported from single randomized or nonrandomized studies. Level "C" evidence data is supported via expert opinion, standard of care or case studies Hirsch et al. (2006).

Vascular history and physical exam class one recommendations are individuals at low risk of PAD and should be assessed by a review of symptoms to assess walking impairment, lower limb pain with rest or present with nonhealing wounds. Class two recommendations are asymptomatic individuals at risk for CLI or PAD based on risk factors such as smoking, HTN, diabetes, dyslipidemia and atherosclerosis. Class three recommendations are symptomatic individuals at risk for CLI or PAD with diagnostic results which may be suggestive of ischemia Hirsch et al. (2006).

Clinicians must determine patients at risk or patients who present with ischemia by determining the extent of the disease and the possibility of restoring circulation to prevent irreversible tissue or nerve damage to ensure positive long-term results. It imperative that clinicians understand the treatment and prognosis varies with, clinical presentation, anatomic site

of claudication, comorbidities, patient compliance and length of ischemia. Studies have shown increased limb amputation may be contributed to lack of diagnoses and timely referral to vascular interventionists due to the inability of primary care providers to recognize individuals who are asymptomatic or whom present with intermittent claudication. It has been recognized that intermittent claudication is the most common symptoms in patients with PAD Hirsch et al. (2006).

The San Luis Valley Diabetes Study conducted a meta-analysis to evaluate and diagnose PAD in diabetic patients using an ABI score. Normal ABI is a score $\geq$ 0.90-1.30. A score of 0.89-0.41 is mild to moderate peripheral disease and a score of $\leq$ 0.40 indicates severe disease with a 95% sensitivity and 100% specificity. ABI results conducted during the study of patients diagnosed with PAD included a score of 0.90 at rest, 0.73 post exercise, and 0.78 after reactive hyperemia which showed a prevalence of 13.7% recognized as diagnostic criteria Hamman et al. (1989).

The Rotterdam Study, a population study in which concluded 7715 patients greater than the age of 55 (60% women, 40% men), was conducted to measure the dominance of asymptomatic patients diagnosed with PAD using ABI as diagnostic criteria. Results concluded symptoms of intermittent claudication was reported in 19.1% with a of 95% confidence interval (CI) 18%-20%, 70% being men and 20% being women and only 6.3% of those indicated symptoms of claudication to support that a majority of patients with PAD show no signs of claudication symptoms Hirsch et al. (2006).

Data within the ACC/AHA guidelines indicate patients age 49-70 with comorbidities and risk factors of PAD to include a history of smoking, HTN, diabetes, dyslipidemia, and atherosclerosis be classified as high risk for PAD and should receive treatment to reduce risk

reduction comparable to those with CAD regardless of lack of symptoms Hirsch et al. (2006). PAD can be a slow process allowing the body to provide collateral circulation which impedes tissue of lower extremities from receiving adequate blood supply and impeding classic symptoms of CLI. Therefor the burden for early detection and diagnoses of PAD should be placed on PCP's as they have a better patient history and patient provider relationship to provide lifestyle recommendations, education, screening and management of comorbidities. Most importantly, PCP's must not presume that all patients with PAD may not show classic symptoms of claudication or LLI. Claudication is defined as pain, discomfort or fatigue of muscles mostly involving lower extremities with exertion. Classic signs include muscle cramping or pain of the lower extremities that present with exertion or exercise and are relieved with three to five minutes of rest. CLI is defined as limb pain that presents at rest or compromised blood flow that may cause loss of limb. Prevention of critical limb ischemia which may present with intermittent pain at rest, cold limbs, ulceration, or gangrene should be a primary goal of all clinicians to prevent irreversible tissue or nerve damage and limb salvage to include referral to vascular specialist Hirsch et al. (2006).

Class one recommendations of the ACC/AHA indicate that patients with CLI receive immediate evaluation and treatment of factors that may increase risk of amputation and those who have previously received successful treatment be evaluated biannually due to high risk of reoccurrence Hirsch et al. (2006).

A vascular surgeon by the name of Dr. Julio Sanguily of Martin Health Systems (MHS), Stuart Florida concluded that the number of lower limb amputations performed annually in diabetic patients with PAD and present with CLI estimated between 160,00 to 180,000. Dr.

Sanguily also found that more than 50% of these patients had no diagnostic or therapeutic endovascular intervention performed in the year before amputation (Sanguily, 2016).

Approximately 18 million Americans suffer from PAD. An estimated two million of these patients suffer from CLI. Patients with CLI have an amputation rate of roughly 40%. Approximately 25% of those patients have a mortality rate within the first year of amputation and a 40% mortality rate within 18 months (Sanguily, 2016).

Sanguily concluded in his study from 2000 through 2010 that of 17,463 patients with PAD 31.6% did not receive arterial testing within the year before LEA. He also found that arterial testing should be offered to patients referred for significant amputation, due to new research to support that revascularization is reducing amputations while improving survival and quality of life. Also, patients with CLI undergoing diagnostic angiography have a 90% chance of lowering the odds of having an amputation (Sanguily, 2016).

Dr. Sanguily led a multidisciplinary approach to his patients at MHS within a five-year period from 2010 to 2014. He concluded that the number of CLI patients who received an angiographic assessment increased from 84 to 500, while the number of number of significant amputations decreased from 24 to 5 and lowered the amputation rate from 29% to 1%. Since 2010, with new technology and techniques, Dr. Sanguily has a 90% success rate in limb salvage (Sanguily, 2016).

Sanguily's protocols consist of using an angiogram in patients who present with PAD, which is an X-ray to assess blood flow through the arteries. Then if needed, patients undergo a procedure to clear blocked arteries. Sanguily explained that the incidence of significant amputation fell 75% with increased use of angiography. Treatments used to remove the plaque include angioplasty and other minimally invasive therapies such as atherectomy, a roto-rooter

type device that cuts plaque away from the artery. In some cases, a stent or small mesh tube is placed to keep the artery open. Also, hyperbaric oxygen therapy helps heal wounds that won't heal (Reinberg, 2015).

Who is a Potential Candidate? Who will benefit?

Ultimately those who are potential candidates and benefit from revascularization intervention are those classifies as high risks and comorbidities include elderly patients, patients 49-70 years of age with any of the following risk factors to have a history of smoking, diabetes, HTN, dyslipidemia, and atherosclerosis regardless of symptoms.

Patients need to be classified according to symptoms, risks and comorbidities so that clinicians may provide appropriate treatment to increase limb salvage and so provide patients with best prognosis and quality of life. Data supports that patients with CLI have a considerably unfavorable prognosis concluding that 40% of patients will require lower limb amputation within six months if no attempt at revascularization is performed and 40% of those will be deceased within 18 months (AHA/ACCF, 2009).

Patients expected to live more than two years based on their other comorbidities should usually be offered bypass surgery first. Patients expected to live less than two years should usually be offered angioplasty and stent therapy first as these patients are not likely to reap longer-term benefits of bypass. Angioplasty will also benefit these individuals as the procedure is less invasive and significantly less expensive. Many patients who cannot undergo a venous bypass should first receive balloon angioplasty prior to prosthetic bypass. Surgeons should make a consciences effort to harvest available veins and consider prosthetic material as a last resort due to a higher incidence of success and longevity reduction of reclusion (AHA/ACCF, 2009).

Studies have shown that patients who are more compliant with lifestyle modifications, smoking cessation, diet, exercise, glucose control, blood pressure control, lipids management and antiplatelet therapy when indicated will have a more favorable prognosis with PAD. A genome test should be indicated for patients receiving Plavix to ensure metabolization and prevent premature stenosis.

Cost of Limb Salvage vs. Amputation

Diabetes is the leading cause of non-traumatic limb amputations due to claudication and lower limb ischemia in the United States. According to the Centers for Disease Control and Prevention, roughly 73,000 diabetic patients received lower limb amputations in 2010. With the rapidly increasing number of patients being diagnosed with diabetes, the number of limb amputations are projected to be around three million by the year 2050. Limb amputations accounted for roughly $11 billion dollars in the year 2014 and approximately 80% of those costs were covered by Medicare (Margolis, 2011).

A six-year cross-sectional comparative cost analysis was performed from 2004 through 2010 to estimate the rapidly increasing healthcare costs of lower limb amputations in diabetic patients who present with PAD and CLI. The analysis concluded 3,381 diabetic patients who received lower limb amputations. In 2004 data concluded that an annual cost per patient was $50,351 (95% confidence interval [CI] = 48,939-51,803); the total cost for all 3,381 patients was $170,236,037. In 2010 data concluded that cost per patient increased to $60,647 (95% CI = 59,143-62,188), with a total cost of $206,380,331 for 3,403 patients. This study suggests that limb amputation is quite expensive and costs are rapidly increasing annually. Therefore, a higher quality of care, to include early diagnosis and intervention in diabetic patients with PAD and CLI

may be an alternative benefit to increase limb salvage and reduce healthcare costs for diabetic patients with PAD and CLI Franklin et al. (2014).

A retrospective economic analysis performed in Sweden concluded that diabetic patients with foot ulcers who were treated with a multidisciplinary approach were associated with much lower healthcare costs compared to those patients who underwent lower limb amputations. The study included a total of 314 patients. In those patients 197 healed with intervention and no amputation, 77 underwent lower limb amputations and 40 died prior to any intervention or amputation could be performed. Total costs were SEK 51000 (3000–808000) for patients with primary healing and SEK 344000 (27000–992000) for healing with amputation. Costs for inpatient care concluded 37% of total average costs for primary healing and 82% for patients with amputation. Costs for outpatient care out-patient care were 45% of the total average cost for primary healed and 13% for patients who healed with amputation Apelqvist et al. (1994).

A ten-year meta-analysis conducted by Barshes et al. (2012), compared interventional revascularization with lower limb amputations in diabetic patients with limb ischemia and their cost effectiveness. The study concluded that endovascular procedures reduces costs by 42% when compared to amputations. Thus, revascularization intervention is more cost effective than amputation.

According to (Yost, 2016), in 2014 total amputations cost $28.2 billion. The total annual number of minor amputations (toe, foot) performed were 134,000, accounting for $17.6 billion with average costs per patient averaging $112,000 for toe, and $261,000 for foot. The total annual number of major amputations (above the knee, below the knee) were 80,000, accounting for $10.6 billion with average costs per patient averaging $128,000 for above the knee amputation, and $188,000 for below the knee amputation. Approximately 25%-33% of patients

with CLI had amputations. Approximately 51%-71% of patients with CLI had no angiogram even though it is estimated that angiogram decrease LEA by 90%. Approximately 60%-71% were unable to have revascularization intervention.

According to Yost, (2014), post amputation average lifetime cost of caregiving was estimated at $300,000. Unreimbursed costs ranged from $81,000-$91,000 with only 100 days reimbursed by Medicare. Medicare costs accounted for 58%, Medicaid costs accounted for 13%, and private insurers accounted for 18%.

Discussion

A review of available literature to date reveals that diabetes has become a global pandemic. With such a rapid influx of newly diagnosed individuals with diabetes each year, we can expect to see comparable increase in healthcare costs and a domino effect of comorbidities to include PAD, CLI, and limb amputation. Unfortunately, data also supports that multiple factors are to blame for such poor prognoses of diabetic patients with PAD and CLI. Such factors include poor patient compliance, lack of screening and diagnoses due to failure to recognize patients who are at risk lack of early intervention, as well as increasing costs of care.

Data provided also indicates that appropriate screening, diagnoses, treatment and management by using a multidisciplinary approach can not only increase limb salvage and improve quality of life but decrease healthcare costs. However, it appears that without a multidisciplinary approach from healthcare providers, and implementation of an adequate lifestyle change and patient compliance via the patient, early intervention will have no benefit and only continue to increase healthcare costs. From current data gathered and literature reviewed, there is sufficient evidence to support the theory that early detection and intervention

would be beneficial to the patient by increasing limb salvage, improving quality of life and ultimately reducing healthcare costs in treatment and management of diabetes and PAD.

Cost-effectiveness will depend on patient compliance, along with clinicians and other healthcare providers adopting a multidisciplinary approach to ensure efficient and effective care. Clinicians must continue their education in order to stay up to date with new guidelines and technology. PCPs carry the burden of being able to identify and classify patients so that they may receive the most appropriate plan of care. If patient compliance is good, early diagnosis is achieved and proper referral to vascular specialist is coordinated, revascularization and management will be successful in limb salvage, quality of life, and will reduce long-term costs. If compliance is poor and early management is not obtained, prices will skyrocket, amputation of lower legs will take place within five years even with early intervention, and death will most likely occur within the next two to two years.

What is The Key to Success?

According to Sanguily, the key to reducing amputations is first to educate PCPs on how to identify and classify high risk patients. Intermittent claudication is the most common cause of PAD, and many of those patients do not show classic symptoms of CLI; clinicians need to be able to identify risk factors and comorbidities. Those patients then need to be referred to vascular specialists prior to irreversible tissue or neuro damage for intervention to have optimal success and limb salvage (Reinberg, 2015).

Dr. Vicken Pamoukian, director of surgery at Lenox Hill Hospital in New York City, concurred that proper education of patients, physicians, and treatment with specialized advanced

facilities with a team approach will benefit patients with PAD and patients could have outcomes superior to what is commonly seen today (Reinberg, 2015).

Keys to Success:

1. Physician education (Self and Referring).
    - Attend training programs focused on the latest advances in peripheral intervention techniques such as Angiosome Guided Therapy, CTO crossing techniques, Asahi wires, Journey wire, Run through, Glide wire Advantage, Quick cross, Navi Cross, CXI Tibiopedal access, and Arterectomy treatment (Ca+).
    - Look beyond the one-hour case, early detection according to risk factors is key.
    - Educate PCPs treating patients at high risk for PAD (most commonly elderly and diabetics). These clinicians also include Podiatry, Nephrology, Infectious Disease, ER, Hospitalist/Internist, and Midlevels.
    - Detection technology using duplex Doppler ultrasound, cap analysis, and ultrasound correlation.
    - ABI, exercise ABI and TBI.
    - Angiography, CTA, MRA.
    - Segmental pressure examination.
    - Angiosome: Selective angiographic arterial treatment.
    - Leading edge technology and staying up to date.
    - Compare treatment and limb salvage algorithms with other peers.
2. PAD/CLI awareness
    - Educate patients with other treatment options as well as PAD/CLI awareness program including diagnosis and treatment of PAD.

3. Multidisciplinary team approach.

- Establish multidisciplinary team approach for limb salvage.
- PCP
- Endovascular Specialist and Team
- Podiatry
- Infectious Disease
- Wound Care Specialist
- HBO (hyperbaric oxygen chambers)
- Midlevel Providers (ARNP, PA-C)
- Nutrition
- Diabetes Educator

Educating physicians who treat elderly, diabetic, and insufficient renal patients is a crucial focus area due to comorbidities common in CLI. Also, physician awareness of PAD, CLI, and treatment options could result in earlier detection and diagnosis which would allow physicians to refer patients to seek early treatment, which is key for limb preservation. A study conducted by Rogers and Chopra concluded that only 42% of primary care physicians and nephrologists were well educated on risk factors of PAD, 60% did not refer patients with lower extremity wounds to PAD specialists, and 72% did not refer patients with diabetes to specialists for vascular assessment (as cited in Sanguily et al., 2016).

Revascularization programs should focus on the latest advances in atherectomy treatment of calcified plaque, angiosome-guided therapy, chronic total occlusion crossing techniques, and tibiopedal access. These programs should not only train vascular surgeons but PA-Cs, ARNPs,

and nurses to form a multidisciplinary approach, which will help raise staff awareness of high-risk patients to educate them on program goals, recognition of PAD and CLI.

Patient education on PAD risk factors is also a priority. Such education should include diabetes education, wound management, wound assessment and diet. Early detection is key to successful revascularization and management.

Patients must understand that PAD can only be managed, not cured. Symptoms are treated to improve quality of life and avoid amputations. Patients diagnosed with PAD must be monitored closely at three, six, nine, and 12 months post-intervention by duplex ultrasound and then once a year after that for the rest of their lives. Furthermore, patients need to understand that without lifestyle modifications to include compliance with treatment of diabetes, cholesterol and smoking cessation, they are still high risk for LEA.

Is Early Intervention Vascular Therapy and Limb Salvage for Diabetic Patients with PAD Cost Effective?

As Americans, we know healthcare can be expensive and cost lots of money. We also know those diabetic patients associated with other risk factors and comorbidities that may include hypertension, dyslipidemia, PAD, CLI, heart failure, kidney disease, among others that can drive healthcare costs through the roof. We know that major amputation is associated with a high rate of mortality and morbidity as well as high revision rates. Complications can increase length of stay in hospitals and increase costs of the overall treatment. Five percent to 10% of below-knee amputees and 15% to 20% of above-knee amputees die in the hospital. (Sanguily et al. 2016). From a financial standpoint, preventative healthcare that improves patients' quality of life would have to decrease the cost of healthcare for those patients.

Most procedures are covered by health insurance plans, including Medicare. The cost of amputations to Medicare and other insurers exceeds more than $11 billion per year (Margolis, 2011). However, arguments have been made that doctors are billing Medicare millions of dollars for unnecessary procedures to open arteries in patients' legs. According to a report via the New York Times, doctors believe that PAD can be treated with exercise and medication, with only about 10% of patients requiring procedures to prevent amputation. However, the doctors that provide these procedures claim that PAD is underrated and costs are lower when a patient's leg is saved rather than amputated (Creswell et al., 2015).

This controversy creates a dilemma between patients, healthcare providers, pharmaceutical companies and insurance companies because so many factors can determine patient outcome. Providing preventative care, such as early revascularization procedures in diabetic patients with PAD would ultimately have the potential to decrease costs, but research has shown that outcomes are solely determined by patient compliance to his or her plan of care. Research has shown that compliant patients not only improve quality of life but decrease healthcare costs. If patients are non-compliant, then healthcare costs are increased on procedures which are ultimately considered a wasted expense because patients relapse as a result and have no increase in quality of life.

Applicability to Clinical Practice/Policy

PAD is a prevalent systemic atherosclerotic disease that associates with other comorbidities with a high risk of mortality. PAD often impairs patient’s quality of life and if not treated early can lead to limb amputation. Although PAD can be accurately diagnosed with ABI and other noninvasive diagnostics, research suggests a high probability that it remains

underdiagnosed and undertreated. It is imperative that healthcare providers make every effort to detect the disease at an early stage and refer the patient to vascular specialists to assess associated risk factors and provide appropriate care. Aggressive management of atherosclerotic risk factors, lifestyle modifications, the use of antiplatelet agents and, early surgical revascularization are the keys for successful control.

Throughout the research, most data conducted on the matter was ten or more years outdated. The outdated analysis did not show significant reduction in limb amputations or death with revascularization in diabetic patients with PAD and CLI. Therefore, the healthcare community as a whole has not yet embraced the idea of early revascularization and fail to prioritize early detection due to lack of screening of asymptomatic patients. Remember, CLI is a slow process and collateral vessels may produce insufficient blood flow to lower extremities that may suppress typical symptoms of claudication.

There is little new research in revascularization intervention. However, the data I concluded strongly supports that with the use of new technology and techniques, early detection and revascularization intervention has become significantly successful for reducing limb amputations and improving quality of life for patients with salvageable limbs. Once more scientific data becomes available, new guidelines and recommendations will implicate the necessity of early detection and early revascularization interventions in patients with PAD and CLI.

Among the new advancements in technology used to clear plaque is the CSI atherectomy device used to clean the inner lining of the calcified artery. Lower profile catheters, wires, and balloons are used on smaller arteries such as those located down in the foot to scale away plaque. Dr. Sanguily (2006) stated that “advancements in technology allow surgeries that were

unimaginable 10 to 15 years ago allow us to re-establish circulation in extremities that were once routinely amputated." For these reasons that Dr. Sanguily has mentioned, along with the data he has gathered to support his statement and the cutting edge of new technology we can prevent limb amputations and improve quality of life in patients with PAD.

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