DIABETIC FOOT ULCERS:
THE IMPACT OF POOR GLUCOSE CONTROL ON OUTCOMES OF TREATMENT

by

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ABSTRACT

Diabetic foot ulcers are a difficult clinical entity. The healing is often delayed due to a number of factors. We also propose in this work the concept of the six detriments to healing a DFU (poor glycemic control, infection, failure to offload the foot, poor nutrition, poor vascular supply, deformity and smoking) - a novel method of approaching the treatment of DFUs but also an important consideration of studying this problem as potential confounders in outcome. This work will describe both the literature associated with these detriments to healing as well as attempt to describe their inter-relations. Furthermore, we test the hypothesis that one of the potential detriments to healing (poor glycemic control) has a direct negative impact on the healing of a DFU. This is done through a cohort design study of patients in a single outpatient clinic undergoing treatment for their DFU.

LIST OF ABBREVIATIONS USED

AKA	Above Knee Amputation
BKA	Below Knee Amputation
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Clinical Nurse Specialist
CRP	C-Reactive Protein
CWIS	Cardiff Wound Impact Schedule
DFU	Diabetic Foot Ulcer
DM	Diabetes Mellitus
ESR	Erythrocyte Sedimentation Rate
HbA1C	Hemoglobin A1C
HR	Hazard Ratio
HRQOL	Health Related Quality of Life
HSC	Health Science Center
iTCC	"instant" Total Contact Cast
LOE	Level of Evidence
LTF	Loss to Followup
LUMT	Leg Ulcer Measurement Tool
MCS	Mental Component Summary
MDLUC	Multi-Disciplinary Leg Ulcer Clinic
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PCS	Physical Component Summary
QEII	Queen Elizabeth II
RCW	Removable Cast Walkers
REB	Research Ethics Board
RR	Relative Risk
SD	Standard Deviation
SF-36	Short Form-36
TCC	Total Contact Cast
WBC	White Blood Cell

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CHAPTER 1 INTRODUCTION

All branches of medicine have a particular condition or pathology that is a challenge to manage. Perhaps it is because the patient population has psychosocial factors that make meaningful change in a condition difficult to accomplish; or, perhaps it is because the pathophysiology is complex and poorly understood making successful treatment a far reach.   In many circumstances both factors may be present.

For a foot and ankle surgeon, some of the most difficult patients to treat are those with a diabetic foot ulcer (DFU). To begin, they often have a chronic and long-standing medical problem. They present to a physician when the wound has been present for weeks or months. These patients frequently have other co-morbidities such as cardiac and renal disease and spend a great deal of time at hospitals and clinics for ongoing care. These patients generally require a substantial investment in time by the surgeon. Their initial appointment may last many times over the normal orthopedic visit duration and they will need to be seen as often as every several weeks. These patients may also have challenging social circumstances that make patient driven change difficult.   The treating physician will need to rely on many other consultants for their expertise - which can be difficult to coordinate. Finally, it will often be difficult to evaluate whether meaningful improvement is occurring with the DFU. Yet, it is difficult to imagine a patient population that

stands to benefit more from coordinated care than the population of patients with a DFU or, stated in another way, a 'foot at risk'.

Diabetic foot ulcers have not been well studied in the literature, which is likely due to the complexity of the problem. This research takes a first step towards better categorizing the problem and proposed treatments. It represents an attempt to place DFUs into the context of rigorous scientific study – by proposing a well-defined research question, scientifically sound methodology, and interpretation of results. But furthermore, this project represents a template by which other clinical questions surrounding DFUs can be studied.

The background section of this work puts into context the severity and burden of diabetes and DFUs at an individual, regional, and national level. It outlines the costs associated with treating a DFU, and the impact of treatment on health related quality of life, and the role of amputation in this population.

We propose the concept of 'the six detriments to healing a DFU' - a novel method of approaching their management but also an important consideration when studying DFUs, as potential confounders. We summarize the literature associated with these detriments to healing as well as attempt to describe their inter-relationships.

Finally, we test the hypothesis that one of the potential detriments to healing has a direct negative impact on the healing of a DFU. This is done through a cohort design study of patients attending a single outpatient clinic, undergoing treatment for their DFU.

CHAPTER 2   BACKGROUND

2.1 DIABETES MELLITUS

Diabetes Mellitus (DM) is a metabolic disease characterized by an abnormal, persistent elevation in blood sugars. It is a chronic condition and left untreated the elevated blood sugars have a deleterious effect on many body organs.

There are several types of diabetes. Type I diabetes occurs when the pancreas fails to produce insulin. It was previously referred to as insulin-dependent diabetes or juvenile diabetes, but these descriptions have fallen out of favour as Type II patients may require insulin and may also be found in the pediatric population.

Type II diabetes occurs when there is an inappropriate response to the produced insulin, occasionally referred to as insulin insensitivity. This is the most common type of diabetes.

Gestational diabetes is an often-transient condition in patients who have not previously been diagnosed with diabetes, which lasts the duration of pregnancy. The cause of gestational diabetes is still not clear but is assumed to be due to pregnancy-related factors. However, both mother and infant are at increased risk of developing Type II DM.

DM has become a serious health problem in Canada. Most recent statistics made available by the Canadian Diabetes Association suggest that 7.6% of the Canadian population has been diagnosed with DM, which represents 2.7 million people[1]. This number is projected to increase with an estimate that 11% of the population (4.2 million people) will be living with DM in 2020. The rate of increase in of DM in Canada has been substantial. In 2000, the prevalence of DM in Canada was 4% (1.3 million people)[1].

There are identified high-risk populations for DM. Increased rates of diabetes are seen among South Asian, Southeast Asian, Aboriginal, Black and Latin American persons. The age-adjusted prevalence rates of DM in the First Nations populations are 3.5 times the national average for men and 5.6 times the national average for women[2]. First Nations are also at significantly higher risk for complications associated with diabetes. In a single study up to 89% of First Nations patients had adverse consequences associated with their DM [3].

Diabetes mellitus has an effect on multiple organ systems. Prolonged exposure to high blood glucose has a toxic effect on peripheral nerves, blood vessels, kidneys and the eyes. The result is neuropathy, vasculopathy, retinopathy, nephropathy and a compromised immune system. Each of these dysfunctions places the foot of a diabetic patient at significant risk.

The peripheral neuropathy develops in a glove and stocking distribution. The most distal or peripheral nerves are affected first and the neuropathy slowly ascends. The first location of neuropathy is in the feet. This results in a loss of protective sensation. In a sensate foot, a small cut, abrasion, blister or area of skin compromise is felt and the natural response is to address it – whether that be by changing of shoe-wear, position, or protection. Patients who attend diabetes education sessions learn that they must be checking their feet daily to ensure that an insignificant injury to the foot, does not result in limb loss.

If a small area of skin compromise is unrecognized due to neuropathy, the wound may develop into a diabetic foot ulcer. By definition, a DFU is a complication of DM. It is a wound on the foot where the healing has been delayed, greater than 14 days. There are many potential causes for the wound – the sources may either internal or external. It occurs in patients who have neuropathy and an impaired capacity for healing (immune compromise and or vasculopathy). This difficult situation may be further compounded by deformity (eg. Charcot arthropathy) and infection. The full spectrum of complications secondary to DFU includes: neuropathic pain, deformity, ulceration, superficial or deep infection, and necrosis, that may ultimately result in amputation.

2.2 GLUCOSE CONTROL AND DIABETES MELLITUS

There are a number of ways to diagnose DM. All require evidence of

significant hyperglycemia. According to the Canadian Diabetes Clinical Practice

Guidelines 2013, the following laboratory values confirm the presence of DM:

- Hemoglobin A1C ≥ 6.5
- Fasting Blood Glucose ≥ 7.0
- 2 hr 75 gm Oral Glucose Tolerance Test ≥ 11.1
- Random Blood Glucose ≥11.1

A random blood glucose is a blood draw that occurs without fasting. Diagnosis of

diabetes from this technique is usually confirmed by a fasting test or oral glucose

tolerance test. However the premise is that only patients with significantly

impaired glucose homeostasis will have a blood glucose value well over 11.0. The

oral glucose tolerance test (OGTT) is a challenge to glucose homeostasis, where

patients ingest a fixed amount of glucose and serum glucose values are checked two

hours post challenge.

Hemoglobin A1C, or glycated hemoglobin, is a type of hemoglobin that is

formed when hemoglobin is exposed to plasma glucose. As a test, hemoglobin A1C

(HbA1C) is a measure of the average blood glucose over the previous 80-120 days.

A value greater than 6.5 is abnormal and diagnostic of DM.

The measurement most relevant to this research paper is that of HbA1C.

Persistent elevations in HbA1C after a diagnosis of DM is made are predictive of

complications associated with DM and mortality. An elevated HbA1C greater than 6.5 has been shown to be a risk factor for the development of a DFU – likely secondary to the impaired circulation that is caused as well as the deleterious effect on peripheral nerve function[4]. It is also associated with the presence and prognosis of infection in a DFU. Furthermore, an elevation in HbA1C > 8.0 has been shown to have a linear relationship with all non-fatal complications of diabetes. If you consider both mortality and non-fatal complications, a bimodal distribution of complications is seen at HbA1C values <6.0 and >11.0 [4].

2.3 DIABETIC FOOT ULCERS

The burden of a non-healing or delayed-healing ulcer is significant. International statistics indicate that 1 in 5 patients with DM will develop a foot ulcer[5]. Statistics related to number of persons living with a DFU in the country are not readily available. But, the average healing time of a DFU is reported to be 165 days[6]. One outcome measure that is monitored however is amputation rates.

The percent of non-traumatic limb amputations that is the direct result of diabetes is between 70-85%[5]. The national amputation rate in Canada is 15 per 100000[1]. Fifty percent of the patients who require a limb amputation for this cause will require a second amputation within 5, years and 30 percent will die within 1 year of amputation[5].

2.3.1 Diabetic Foot Ulcers and Amputations

Not all amputations carry the same impact for a patient. Grossly, limb amputations can be categorized as either major or minor. Minor amputations, such as disarticulation at the metatarsophalangeal level (toe amputation), ray amputation (removal of a single or multiple toes and a portion of the corresponding metatarsal bone) or a transmetatarsal amputation (forefoot amputation) are well tolerated functionally. Toe disarticulations allow the patient to return to normal shoe-wear and independent ambulation. Ray amputations require silicone or other prosthesis only if attempting to achieve higher levels of functioning such as sporting activities[7]. Isolated loss of the hallux has little impact on the day to day activities of patients. Transmetatarsal amputees have the highest level of disturbance to their gait and push-off strength, of the minor amputations. One study noted a 73% incidence in ability to return to independent ambulation[8]. The major complication of a minor amputation is the rate of non-healing.

The same factors that put an ulcer at risk of not healing affect the capacity for wound closure after a distal amputation. The rate of healing for a toe amputation is not well reported in the literature. Many physicians counsel patients that the chance of non-healing and need for revision or more proximal amputation exceeds 50%. The transmetatarsal amputations have a variable rate of healing in the literature ranging from 37-53% [8, 9]. Failure of an amputation at the distal level

must be considered preopoperatively as many of these patients are poor surgical candidates and repeated operative procedures should be avoided.

Those amputations considered to be 'major' - below knee (BKA), through knee and above knee (AKA) - have higher rates of healing but increased risks of morbidity. The most proximal amputations have the highest rates of healing and the incidence of healing an AKA can be as high as 90% (9). In comparison, BKA healing rates vary between 30 and 90% in individual studies. The rate of conversion to a higher level amputation following a BKA may exceed 30% [10]. The major amputations are also a more significant cardiovascular stress to the individual patient from a surgical perspective.

The significant concern associated with a major lower extremity amputation is the resulting functional status. A study published by Larsson et al. evaluated the functional outcome of patients with diabetes who had a lower extremity amputation and concluded that only a small number of patients regained independent ambulation. This study found that of those patients who were able to walk 1km prior to their amputation, only 19% were able to following surgery. The study also found that 70% of patients with a transtibial amputation who were ambulatory preoperatively were fitted for a prosthesis, but only 50% used it consistently [11].

Many non-healing diabetic foot ulcers go on to require eventual amputation. As indicated above, the outcome of this procedure is variable. On one end of the

spectrum, a minor amputation that heals may be favourable and may spare the patient prolonged treatment for an ulcer. However, it is difficult to predict who will respond favourably to a minor amputation. On the other end of the spectrum, a major amputation is a significant and life-changing event for a patient and places this patient population at significant risk of becoming dependent on a wheelchair to mobilize.

2.3.1 Diabetic Foot Ulcers and Health-Related Quality of Life

Patients who are living with a DFU experience significant alterations in their health related quality of life (HRQOL). The deterioration in quality of life has been demonstrated in studies that compare the results of the Short Form -36 Health Survey (SF-36) to diabetic patients without DFU and other chronic conditions [13]. The SF-36 is a validated measure of global health status [12]. This self-reported questionnaire has eight sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Physical Component Scores and Mental Component Scores are calculated from the above eight components, where a lower score represents a worse measured health than a greater score.

The SF-36 has demonstrated aberrations in the quality of life of patients living with many chronic diseases. A large study, which included eight countries, assessed the amount of disturbance in HRQOL for such chronic conditions as:

allergy, arthritis, hypertension, congestive heart failure (CHF), chronic lung disease,

diabetes and ischemic heart diseases [13]. Congestive heart failure, chronic lung

disease and arthritis demonstrated the greatest disturbances in the physical

summary (PCS) scores. The average PCS score for these three conditions was 47.5

which represents four-tenths of a standard deviation below patients without a

chronic condition (average score 51.9) [13]. While the absolute value of these

numbers may appear small, this same study highlights that this difference (47 to 52)

has been shown to be predictive of a 27% increased likelihood of an inability to

work due to the condition over one year and a 16% increase in mortality over 5

years [14]. This same study (as well as others) demonstrated that patients with DM

(without a foot ulceration) have PCS scores greater than other chronic conditions

such as arthritis, congestive heart failure and ischemic heart disease [15, 16].

   The presence of a DFU has a significant impact on the HRQOL of patients with

diabetes. Ribu et al. [17] looked at a cross-sectional population of patients in

Norway with DFUs who were being treated on an outpatient basis. The results of

their HRQOL (SF-36) were compared to those of the general population and to a

matched group of patients with diabetes but no DFU, from a general census taken by

the Norwegian government. Significant differences (p<0.001) in all eight categories

of the SF-36 as well as the component scores, were noted in the patients with a DFU

compared to both the general population and those with diabetes. The most

significant findings when compared to patients with diabetes alone were

abnormalities in role limitation-physical (32.1 vs. 62.2, p<0.001), physical

functioning (57.5 vs. 77.3, p <0.001), and role limitation-emotional (57.4 vs. 72.0, p

<0.001). The smallest differences between the populations were found in the

mental component scores (DFU – 47.6 vs. diabetes – 49.8 vs. general population –

51.5) but even these were significantly different (p<0.05 DFU compared to diabetes

populations; p <0.001 DFU compared with general population) [17].

Another study, by Goodridge et al. [18], compared the HRQOL scores from

the Short Form-12 (SF-12) and the Cardiff Wound Impact Schedule (CWIS) of

patients with healed and unhealed ulcers. The SF-12 is a shortened form (12 items)

of the SF-36. Multiple studies have demonstrated that the SF-12 in comparison to

the SF-36 has the ability to reproducibly obtain comparable outcomes for the MCS

and PCS scores [19, 20]. Their results demonstrated that patients with an unhealed

ulcer had lower physical component scores (PCS) on the SF-12 compared to those

with a healed ulcer (unhealed, 35 ± 8 points; healed, 39 ± 10 points; p = 0.04). The

PCS scores of the patients with an unhealed ulcer were also lower than reported

values for patients with DM, HTN and the general population [21, 22]. The CWIS is a

disease-specific health related quality of life measure that has been validated in the

DFU population [23]. Scores from the CWIS in this particular study identified

frustration over the ulcer healing and anxiety surrounding the treatment with a

resultant lower well-being component score (35 ± 6 points)(17). There have been

differences documented in the CWIS score of patients with a healed compared to

unhealed ulcer: social life (p<0.001), physical symptoms and daily living (p<0.01)

and finally well being (p<0.001) [23].

It may be concluded that disturbances in health-related quality of life are quantifiable and significant in patients with DFUs. The disturbance is greater than in those patients with diabetes but without foot ulceration and comparable to other chronic health conditions, clearly establishing a need to address effectively and efficiently this health problem.

2.4 SUMMARY

In summary, the persistent elevation of blood glucose, known as DM results in multi-organ system dysfunction. This places patients at risk of developing a ulcer on their foot. Once present, these same factors contribute to the delay in healing of the ulcer. The incidence of DFUs in the Canadian and global populations is not insignificant and deserves special attention by clinicians and researchers. Patients with DFUs are a significant burden to the Canadian Healthcare system and experience significant alterations in their HRQOL. The presence of a long-standing ulcer places the patient at risk for needing amputation surgery, which carries a series of risks and complications as well as social challenges. Clearly, there is a burden to improve care with respect to this patient population.

CHAPTER 3   DETRIMENTS TO HEALING A DIABETIC FOOT ULCER

3.1 THE CONCEPT

The treatment goals for patients with a DFU are to heal the ulceration and produce a plantigrade and stable foot to allow activities of daily living and improved health related quality of life without ulcer recurrence.   These goals may be simple to enumerate but are often difficult to achieve.

The healing rate and time of diabetic foot ulcers has been shown to be delayed - although there is variability in the reported healing times. Ince et al. studied 410 ulcers in 154 patients and found a median healing time of 63 days (range 18-1486) in the 91% of ulcers that healed [6]. Of the ulcers studied, 59% were healed by week 12, 71% by week 20 and 87% by week 52. This is comparable to a study by Piaggesi et al. that demonstrated a healing rate of 79% by 6 months [24], but is significantly slower than what is described by Katz in a comparison of off-loading techniques whereby a healing rate of 74 and 80% in the two study arms was found at 12 weeks [25]. In comparison, healing of a traumatic or surgical wound is considered to be delayed if it is unhealed after 14 days.

There are a several generally accepted factors that may act as deterrents to wound healing, and more specifically, diabetic foot ulcers. These include:

1. Deformity
2. Plantar (or External) pressure
3. Vascular pathology
4. Infection
5. Elevated blood sugars
6. Smoking
7. Poor nutrition

It is not novel to consider that each of these individual factors may contribute to the delay or non-healing of a wound or ulcer. However, the concept that there are a inter-related factors that may be contributing to the non-healing of a DFU, to address these clinically and to consider them as potential confounders in a study is, to the best of our knowledge, not yet described in the literature.

In order to validate this concept, a summary of the evidence behind the detriments to healing a DFU was undertaken. This was to validate the reversal or optimization of each of the detriments to healing a DFU in the clinical setting. A research question (ex. Does deformity correction improve DFU healing?) and hypothesis (ex. The literature will support deformity correction as a treatment to improve rates of healing of a DFU) was assigned to each detriment to healing. The relevant search terms were defined for each detriment to healing (employing both Mesh and Non-Mesh terms) from the hypothesis and research question. A list of the research questions and hypothesis for each of the potential detriments to healing a DFU are listed in Appendix A. A separate literature review was performed using PubMed for each of the research questions. Articles were considered for inclusion

in the review first based on the title, then the abstract and finally the full article.

Articles were excluded if they failed to answer the research question or were not

available in English. Included articles were assigned a level of evidence (LOE) as

described by Wright et al. [26, 27]. Included articles were also noted to either

support, or refute the hypothesis. The total number of articles by LOE were

summated and the percent in agreement with the hypothesis was reported. The

total body of evidence was assigned a grade of recommendation according to the

technique described by Wright et al [26, 27]. This summary of the evidence behind

each of the detriments to healing a DFU is described below.

3.1.1   Deformity

A foot deformity may be present in a number of forms in patients with a DFU.

Common deformities of the forefoot include clawtoes, hammertoes, overlapping

digits, and a hallux valgus deformity. Midfoot and hindfoot deformities found

commonly in patients with diabetes would include pes planus, rockerbottom

deformity (Charcot arthropathy) and/or a tight tendo-achilles. Furthermore,

previous amputations may also contribute to a deformity. A deformity changes the

distribution of force and weight throughout the foot.

A normal or plantigrade foot is commonly described as providing a tripod

distribution of weight. More precisely, however, peak forces (or weight

distribution) is localized to the heel and underneath the second metatarsal head.

More than 60% of the weight is disbributed to the rearfoot and 28% to the forefoot in a standing position. The distribution of weight and therefore pressure in the forefoot fans out from the second metatarsal head along an axis roughly bisecting the five metatarsal heads. The pressure changes during walking and running. Whereby most of the pressure weight is distributed to the hindfoot during barefoot standing, the pressure accelerates rapidly across the midfoot and then to the forefoot with gait. Peak pressures are obtained at 80% stance phase (under the second metatarsal head) and then progress to the hallux. Overall, the peak forces that occur in the foot are substantial, achieving 120% body weight during walking and 275% body weight with running [28]. A change in the shape of the foot results in the abnormal distribution of weight through the foot, with the risk of skin breakdown on the plantar surface of the foot, and may prevent an ulceration from healing due to ongoing trauma through weightbearing.

Each type of deformity likely carries a different risk and role with respect to the non-healing of a DFU. A clawtoe deformity places increased pressure under the associated metatarsal head, but also places additional pressure on the dorsal soft tissues when in shoewear. A rockerbottom deformity will create overloading of the midfoot and a tight tendo-achilles increases the forefoot pressures.

A comprehensive review of the literature was performed to answer the following question: Does deformity correction (specifically a tendo-achilles lengthening for a tight tendo-achilles) improve DFU healing? The initial search

results yielded a total of 44 papers, 14 of which were relevant and included [29-42].

A summary of the number of articles by LOE for each detriment to healing (and

percentage of articles in support of the concept that deformity correction improves

DFU healing) is included in Table 1. Of the 14 articles reviewed, one paper was

assigned a LOE I (a single RCT), one article was assigned an LOE III, five articles

were assigned an LOE IV and seven articles were designated as an LOE V. All but

one of the LOE IV papers supported the hypothesis.

Perhaps the most telling article was that of Mueller et al. They performed a

RCT in diabetic patients with a tight tendo-achilles – assigning them randomly to

total contact casting (TCC) alone or in combination with percutaneous achilles

lengthening. All 30 ulcers in the TCC + percutaneous achilles tendon lengthening

group healed at a mean of 58 ± 47 days whereas 29 of the 33 ulcers in the isolated

TCC group healed in 41 ± 28 days (p>0.05). Furthermore, at two years followup

81% of the patients in the TCC group in comparison to 38% of the patients in the

TCC + tendon lengthening group had a recurrence of an ulcer (p=0.002) [40]. At

face value the outcome of this study may seem contradictory. The patients in the

TCC alone group had a lower rate of healing but a shorter time to healing (not

statistically significant). However, the fact that there was a lower rate of recurrence

in patients who had surgery would suggest that true 'healing' of the ulcer was far

more effective with TCC in combination with achilles lengthening as these patients

not only closed (which is perhaps the more precise term to be applied to the healing

that took place at 58 and 41 days respectively) but remained closed and therefore healed.

Ultimately, it could be said that the research question for this particular potential detriment to healing should have been worded differently. As it currently stands, the question asks whether of the deformity (in this case a tight tendon achilles) improves the long-term healing of a DFU. Which is different from asking the question "is deformity a detriment to healing a DFU." We are making the assumption that if reversing the deformity helps with healing than the presence of the deformity was detrimental to healing – which may or may not be correct. However, given the literature available on this topic and the breadth of deformities to consider we attempted to answer the question as simply as possible.

Overall, there is fair evidence (Level II or III studies with consistent findings) that supports performing an intervention to reverse a deformity for the purpose of DFU healing.

3.1.2   Plantar (or External) Pressure

The application of pressure to a wound causes local necrosis or decrease in circulation. This is the basis for the first aid treatment of bleeding – but is detrimental in the case of DFUs. Furthermore, repeated direct pressure to a wound is likely to cause local trauma. Plantar or external pressure may result from many

sources - a normal or plantigrade foot with a plantar ulcer will experience plantar

pressure from weight-bearing on the limb. Other sources of external pressure may

include shoewear, pressure from seating devices (such as wheelchairs) or

positioning (as is more often the case with decubitus ulceration in the immobile

patient). The role of plantar pressure may be worsened by the presence of

deformity as this may result in the abnormal distribution of body weight onto the

foot.

A comprehensive review of the literature was performed in the identical

manner as was described above. The research question for this particular detriment

to healing was whether offloading of the plantar pressure through a total contact

cast improved healing of a diabetic foot ulcer. We assumed that if reversing plantar

pressure improved the rate of healing a DFU, then this factor was a detriment to

healing.

The initial literature search on this topic yielded 180 papers of which 35

were relevant and included [43-77]. Of the 35 papers, three were assigned a LOE I

and one paper was assigned a LOE II. All of the Level I and II papers were in support

of the hypothesis. Four articles were assigned a LOE III and five articles were

assigned an LOE IV – of these articles 67% were in support of the hypothesis.

Finally, twenty-two articles were designated as an LOE V and all of these were in

support of the hypothesis.

Armstrong et al. published two separate randomized control trials that tested the hypothesis that offloading with a total contact cast (TCC) is superior to other forms of offloading [74, 75]. In the first study, published in 2001 patients with non-infected DFUs were randomized to TCC, removable cast walkers (RCW), or half-shoes. Outcome measures were time to complete healing, percent healing at 12 weeks and activity level (monitored with step counts). The patients with a TCC had higher rates of ulcer healing at 12 weeks compared with both the RCW group and those patients assigned to half-shoes (89.5 vs. 61.4%, p=0.026, odds ration 5.4, 95% CI 1.1-26.1). The total steps were comparable between TCC (600 +/- 320 daily steps) and RCW (767 +/- 563; p=0.67) but significantly higher in the group with a half-shoe (1462 +/-1452; p=0.04) [74]. The study authors postulated that the differences in healing rates between TCC and RCW relate to the ability to remove the RCW and therefore the potential non-compliance with pressure offloading.

The second study published by Armstrong et al. was a RCT of an "instant" total contact cast (iTCC) compared to a RCW. The iTCC is a technique which employs a RCW but is secured in such a way that it is not removable by the patient between clinic visits. As with the previous study, significant differences were noted between iTCC and RCW with respect to healing rates. 83% of patients assigned to an iTCC vs. 52% of patients with an RCW had evidence of a healed ulcer at 12 weeks (p=0.02, odds ratio 1.8, 95% CI1.1-2.9) [75]. This demonstrates that offloading through a non-removable pressure distributing device improves healing rates of DFUs.

Morona et al. published a systematic review and meta-analysis of the effectiveness of different off-loading devices in the treatment of DFUs [52]. Non-removable off-loading devices were found to be more effective at treating DFUs than removable devices (RR = 1.43, 95% CI 1.11, 1.84; p = 0.001). Again, this was attributed to patient compliance with the removable devices.

Overall, there is good evidence (Level I studies with consistent findings) in support of offloading as a treatment for DFUs which represents a grade of recommendation 'A'.

3.1.3 Infection

Infections that occur concurrently with a DFU may be either superficial or deep. The spectrum of manifestations may include cellulitis, localized abscess, or osteomyelitis and each may be either acute or chronic. Infection in any wound has a deleterious effect on healing by prolonging the pro-inflammatory environment, disturbing the normal clotting cascade, as well as angiogenesis (and therefore granulation tissue formation), and promoting disordered leukocyte function [78].

A DFU is commonly colonized with multiple organisms, as is the nature of an open wound. Clonization is the presence of microbes without evidence of local or systemic host reaction. Infection occurs with an increase in the bioburden of the

microbes and the resultant response from the host. Clinically, the presence of

infection is associated with local signs such as erythema, purulent drainage, and foul

odour. Systemic signs of a infection include fever, malaise, and in the extreme form

sepsis. Laboratory investigations may be helpful to diagnose an infection.

Commonly a positive culture can be obtained from the wound, and biomarkers such

as an elevated white blood cell count (WBC), erythrocyte sedementation rate (ESR)

and C-reactive protein (CRP) may be present. Treatment of an infected DFU

involves identifying the causative organism(s), appropriate use of antibiotics and

possibly surgical debridement of the area. Infected DFUs are commonly due to an

aerobic gram-positive cocci, but often are polymicrobial [79]. The goal of initial

antibiotic therapy is to provide adequate coverage for the common causative

organisms and then to refine the antimicrobial selection once appropriate culture

results are available.

The role of infection in the non- or delayed healing DFUs was addressed

through a complete literature review (process described in the section above under

"Deformity"). The initial search parameters yielded 264 possible articles, of which

16 were considered relevant and included [80-95]. Of these 16 articles, three were

assigned a LOE III and thirteen were assigned a LOE V.   There was complete

agreement in all of the articles in support of the hypothesis that a superficial or deep

infection was detrimental to the healing of a DFU.

Dos Santos et al [83] performed a retrospective review of 99 patients with DFU to assess for the potential risk factors for amputation (accepted to represent failure of healing of the DFU or sepsis). They found that the presence of gram-positive microorganisms and ascending lymphangitis (odds ratio, OR=2.5) was associated with the need for amputation. Other risk factors for major amputation were: age, arterial insufficiency and location of wound (calcaneal lesions).

Armstrong et al [80] performed a review of 360 patients with a DFU in an outpatient setting. The objective of this study was to validate a wound classification instrument (The University of Texas Wound Classification System). This study found that those patients with a lesion that probed to bone (the hallmark of osteomyelitis) were more than 11 times more likely to receive a major amputation (18.3 vs. 2.0%, $p<0.001$, OR=11.1, CI= 4.0-30.3). Also, those patients with an infection and ischemia were 90 times more likely to require a major amputation compared with those free of infection or ischemia (76.5 vs. 3.5%, $p<0.001$, OR=89.6, CI=25-316).

There is overall unanimous agreement in the literature that infection is detrimental to the healing of a DFU, however, the strength of the literature is poor. This results in a grade of recommendation 'C' in favour of the hypothesis.

Furthermore, the impact of infection on the healing of a DFU is not in isolation of other potential detriments to healing. Poor glucose control has an effect

on the type and severity of the infection present [96]. Smoking is a significant risk

factor for the development of an infection [97] as is poor nutrition [98].

3.1.4   Vascular Supply

The persistent elevation of blood glucose with diabetes mellitus has a direct

toxic effect on both the macrovascular and microvascular circulations. The effect on

large blood vessels is the development of atherosclerotic disease (plaque formation)

and on the microvascular system (capillary network) is, similarly, thickening of the

vessel walls and increased tone of the smooth muscle cells, with resultant

vasoconstriction and propensity for microthrombi. This is mostly due to the

production of nitric oxide from the endothelial cells.

The potential role of poor vascular supply in the healing of a DFU was

assessed through a comprehensive literature review (process described in the

section above under "Deformity"). The initial search parameters generated 295

articles of which 30 articles were considered relevant and included [84, 99-127]. Of

these 30 articles, two articles were assigned a LOE III, fifteen articles were assigned

a LOE IV and thirteen articles were assigned a LOE V. There was significant

discrepancy between articles as to whether or not revascularization of the foot

improved the rates of healing a DFU. 50% of the Level III articles and 93% of the

level IV articles supported the hypothesis.

A large-scale review of the literature was undertaken by the International Working Group on the Diabetic Foot to evaluate the effectiveness of revascularization in patients with a DFU and peripheral arterial disease. This systematic review found that at 1-year follow-up, limb salvage rates were 85% (open procedures) and 78% (endovascular techniques). The group concluded that the studies demonstrated improved rates of limb salvage with revascularization compared to medical therapies [110].

However, a large (917 ulcers) study by Taylor et al [127] found little difference in healing rates for patients with or without ischemia. This retrospective study compared the outcomes of 460 limbs with significant ischemia (219 which were revascularized) to those without ischemia. There was very little difference noted in terms of healing rates for those with or without ischemia (28.5% vs. 26% p=0.4). Ischemia was found to be a significant marker of poor outcome with 5-year limb salvage rates of 80% for nonischemic ulcers, 61% for ischemic ulcers which were revascularized, and 51% for ischemic ulcers not revascularized (p<0.001).

Based on the poor quality of literature on the topic and the degree of heterogeneity in the findings, a grade of recommendation 'C' was assigned to the body of evidence that addresses whether revascularizaiton of a limb improves the healing of a DFU.

Furthermore, the vascular supply of the DFU will be directly influenced by the quality of glucose control. Patients with elevated HbA1C have demonstrated worse vascular pathology [128]. Smoking alone has long been established as having a significant deleterious effect on vascular supply and has been shown to be a significant risk factor for the development of arterial occlusive disease [129]. Finally, vascular supply and infection have a bidirectional effect on each other as potential detriments to healing a DFU. Infection impairs angiogenesis as previously described above, but poor blood supply prevents the body from being able to respond to an infection effectively [80].

3.1.5   Smoking and Nutrition

Smoking and Nutrition are addressed together as they have many commonalities. Both of these potential detriments to healing have poor quality evidence to support their direct involvement in the impaired healing of a DFU. However, if you asked any clinician whether each of these plays a role in the non-healing of a wound the answer would be unanimously in favour of this.

We have already established above that smoking has a deleterious effect on blood supply [129] and increases the risk and severity of infection [97]. Poor nutrition in essence is the precursor for immunodeficiency and has also been established above as a potential causal factor for infection.

Complete literature reviews were performed on each of these topics (in the same manner as all of the previous detriments) to determine if each represented a detriment to healing a DFU. The initial search results for the hypothesis that smoking may be a detriment to healing a DFU resulted in 180 articles. Of these papers, eight articles were considered relevant [130-137] – five of which were assigned a LOE IV and three were assigned a LOE V. Three of the five level IV papers supported the hypothesis.

The same process was applied to the question of whether poor nutrition represented a detriment to healing a DFU. Even less literature was available on this topic. The initial search generated 79 articles, of which only 5 were relevant and included [138-142]. Two articles were assigned a LOE IV and three were assigned an LOE V. Neither of the level IV articles established a causality for poor nutrition as a detriment to healing a DFU, but all of the Level V papers favoured our hypothesis.

Both "smoking" and "poor nutrition" have been assigned a Grade of Recommendation 'I' as there is insufficient or conflicting evidence to support recommendation for or against a particular intervention.

3.1.6   Glycemic Control

Patients diagnosed with diabetes have a persistent elevation of blood glucose as determined by one of several diagnostic tests (fasting glucose, random glucose

testing, oral glucose tolerance testing or HbA1C). The fundamental principle of treatment for diabetes is optimal control of blood glucose – or glycemic control. This is monitored by HbA1C – a test of the glycemic control over the past 2-3 months. The target HbA1C for patients with diabetes is ≤ 6.5.

The primary focus of this research paper is that of glycemic control. We have established that poor glycemic control affects the type and frequency of infection in DFUs [96]. We have also established that poor glycemic control has a negative effect on blood supply to the extremity. The literature review which took place addressed whether poor glycemic control (persistently elevated blood glucose levels) had a direct detrimental effect on healing a DFU.

The same approach was applied as with the above topics. The initial search result generated 270 articles of which 24 were considered relevant and included [103, 130, 140, 143-163]. Of these articles, thirteen papers were assigned a LOE IV and eleven a LOE V. There was not agreement among the papers regarding the effect of glycemic control on DFU healing. 69% of the level IV papers and 90% of the level V papers were in support of the hypothesis.

Marston et al [156] performed subgroup analysis on a previously reported study comparing human dermal substitute to a control treatment. The goal with this secondary analysis was to determine risk factors related to DFUs time to healing and closure. Glucose control was measured in this study by the initial

HbA1C, average HbA1C and change in HbA1C.   The study found that those patients who had an increase in their HbA1C during the study period had a rate of healing of 21% where as those patients whose HbA1C remained stable or decreased had a healing rate of 26.3% (p<0.05).

Adler et al [143] completed a systematic review and meta-analysis that included a total of 14 articles. The LOE that we have assigned to this review represents the quality of studies included in the analysis. This study did find a significant increase risk of lower extremity ulceration for each percentage point increase in HbA1C.   The RR for amputation was 1.26 (95% CI 1.16-1.36) for each change in HbA1C. It was also noted that there was significant heterogeneity across the studies (I^2 76%, 67-86%; p<0.001).

Christman et al [146] performed a retrospective review of 183 patients in an out-patient setting with DFUs. The primary outcome of this study was wound healing rate (measured as cm^2).   In this study, for each point increase in HbA1C, the daily wound-area healing rate decreased by 0.028 cm^2/day (95% CI: 0.003, 0.0054, p=0.027).

Markusson et al [155] performed a retrospective review of 63 ulcers to determine factors that may impact healing of a DFU. With regards to HbA1C and healing, the mean healing time for patients with a HbA1C 4.0-7.0 was 85 days (SD 80 days) compared with 123 days (SD 135 days) for those patients with a HbA1C 7.1 -

10.0. The healing time for patients with a HbA1C greater than 10.1 was 147 days

(SD 173 days). The differences, however, were not statistically significant

(p=0.686).

Winkley et al [162] recruited 253 patients into a retrospective study to

assess whether a number of factors may relate to a negative outcome with respect

to treating a DFU. The negative outcomes of interest were recurrence of ulceration,

amputation and death. They found that having a lower HbA1C was protective

against associated with mortality (HR 0.73, 95% CI 0.56-0.96). No other

associations were identified in this study with respect to HbA1C.

Overall, a grade of recommendation 'I' has been assigned to the body of

literature available to answer the research question regarding glucose control.

There is insufficient and conflicting evidence not allowing a recommendation for or

against the hypothesis, which supports the need for further study on this topic.

3.2 SUMMARY

We propose seven potential detriments to the healing of a diabetic foot ulcer,

supported by our review of the literature. Table 3 summarizes the literature

findings by detriment to healing and Table 4 summarizes the grade of

recommendation assigned to each of the potential detriments to healing a DFU.

Table 1	Number of articles located by Level of Evidence (LOE) for each potential detriment to healing a DFU. Percentage of articles in agreement with hypothesis indicated in parenthesis.

	LOE I	LOE II	LOE III	LOE IV	LOE V
Infection	0	0	0	3 (100%)	13 (100%)
Glycaemic control	0	0	0	13 (69%)	11 (90%)
Vascular supply	0	0	2 (50%)	15 (93%)	13 (77%)
Smoking	0	0	0	5 (60%)	3 (100%)
Nutrition	0	0	0	2 (0%)	3 (100%)
Deformity	1 (100%)	0	1 (100%)	5 (80%)	7 (100%)
Offloading	3 (100%)	1 (100%)	4 (50%)	5 (80%)	22 (100%)

Table 2	Grades of Recommendation for each detriment to healing of a DFU

	Grade of Recommendation	Interpretation
Infection	C	Poor quality evidence (Level IV or V studies with consistent findings) for or against recommending intervention.
Glycaemic Control	I	There is insufficient or conflicting evidence not allowing a recommendation for or against intervention
Vascular Supply	C	Poor quality evidence (Level IV or V studies with consistent findings) for or against recommending intervention
Smoking	I	There is insufficient or conflicting evidence not allowing a recommendation for or against intervention
Nutrition	I	There is insufficient or conflicting evidence not allowing a recommendation for or against intervention
Deformity	B	Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.
Offloading	A	Good evidence (Level I studies with consistent finding) for or against recommending intervention

However, in addition to describing the literatures support for the each of the potential detriments to healing, we have described also the inter-relations that may exist between the potential detriments to healing. This has been expressed in a causal diagram in Figure 1.

Figure 1   The relationships between the potential detriments to healing.

Hyperglycemia is involved in several parts of the causal pathway. An elevated HbA1C is in itself a risk factor for the development of a DFU [164-166]. It has also been associated with an increase in rates of infection as well as more severe infections [96].   The reverse relationship is also true, as severe infection negatively

impacts glycemic control [167]. Poor glycemic control has been demonstrated to have a negative impact on capillary circulation and peripheral nerve function in the diabetic foot [168]. Macro-circulation dysfunction has also been attributed to poor glycemic control [169]. The causal pathway between poor glycemic control, infection and vascular pathology is demonstrated in simplified figure of Figure 2.

Figure 2   Causal pathway between poor glucose control and the associated detriments to healing.
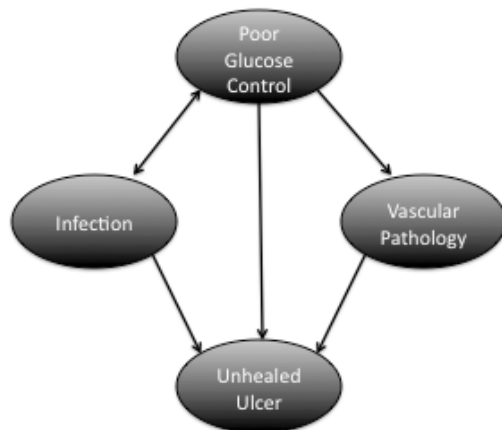
Ultimately there are likely even greater inter-connections than what is described in these causal pathways. What is identified above, is the known relationships between the detriments to healing. It is anticipated that further research into these factors as potential detriments to healing will reveal additional information.

CHAPTER 4   THE RESEARCH STUDY

This research study was undertaken to better understand and treat DFUs. Up to this point, we have demonstrated the significant impact that DFUs have on patients as well as the community at large. We have described the potential factors that may contribute to the problem of the non-healing DFUs. Given the central role of glycemic control in DM management and end organ complications, we elected to study its impact on DFU healing.

4.1 RESEARCH QUESTION

Does poor glucose control (elevated HbA1C) upon presentation with a diabetic foot ulcer have an impact on the time to healing a DFU?

This research question was selected for several reasons. Examining all the detriments to healing was too large a project to undertake within a masters thesis. It was necessary to decide on a starting point. Out of all the potential detriments to healing a DFU, glycemic control was considered to be of key importance. It represents the basic disturbance in the pathophysiology of DM, with poor glycemic control being the reason why complications occur.

HbA1C was selected as the measure for glucose control in this study as it represents the mean glucose control over 2-3 months. Other studies have looked at

whether initial glucose HbA1C (at time of presentation with a DFU), average HbA1C (over DFU treatment period) or change in HbA1C (during DFU treatment) had an impact on rate of healing of a DFU [156]. No study to date has confirmed a relationship between the HbA1C at presentation with a DFU and healing rates of DFUs. However, the initial presenting HbA1C represents the glycemic control over what is likely the interval in which the ulcer developed. The outcome of importance in this study was the time to healing (or closure) of an ulcer.

The objective of the study is to estimate the association between 1) HbA1C values at the time of presentation with a DFU to a multi-disciplinary leg ulcer clinic (MDLUC) at a tertiary care, academic health care center in Halifax, NS and 2) time to healing an ulcer.

4.2 METHODOLOGY

4.2.1 Study Design

We used a cohort study design for this research project. A cohort study is a type of observational study which is used to evaluate associations between diseases and exposures. By definition a cohort study is one where an outcome-free study population is first identified by the exposure of interest and followed until the outcome of interest occurs [170].

The cohort selected for this study is a group of patients attending an outpatient clinic for treatment of a DFU The target population for which this study will be applicable is all patients with a DFU. The available sample is those patients attending the Multi-Disciplinary Leg Ulcer Clinic (MDLUC) at the Halifax Infirmary, part of the QEII Health Sciences Center in Halifax, Nova Scotia. This is a tertiary-care and academic teaching hospital. Patients attending this clinic are largely from the Halifax Regional Municipality – a predominantly urban and sub-urban population of approximately 400 000.

MDLUC sees patients who have non-healing, chronic ulcers to their lower extremities (below knee) of various etiologies. Patients are referred to the clinic by any consultant in one of the following specialties: Plastic Surgery, Orthopedic Surgery, Vascular Surgery, or Infectious Diseases. All other specialties send referrals to one of the services above, where they are triaged as appropriate or not for the ulcer clinic. The clinic is supported by a single Clinical Nurse Specialist (CNS) who attends all clinic days. Staff support is provided by specialty consultants from Plastic Surgery, Orthopedic Surgery, Vascular Surgery and Infectious Diseases who attend one half-day clinic per week. The clinic takes place out of a single physical space (Vascular Surgery clinic).

On the first visit to MDLUC, the CNS completes an Initial Assessment Form (Appendix B) which is an evidence-based tool developed by this author for the

purpose of 1) obtaining baseline patient demographics and the potential detriments to healing and 2) triggering treatment and investigation decisions, including as well as referrals to the appropriate specialists. A comparable follow-up tool is used at subsequent visits (Appendix C). There is fluidity to the care of patients in the clinic by the various subspecialists – that is to say, a patient may be seen on an initial visit by Infectious Disease, but if they are found to have a significant deformity, the next visit is likely to be with the consultant from Orthopedic Surgery. Patients have consistent input on all visits from the CNS, but also have access to subspecialty consultants that attend the clinic.

The exposure of interest in this study is the HbA1C at the time of presentation to MDLUC. Most laboratories will not repeat the HbA1C if a result has been obtained in the prior 8 weeks (as it is a measure of control over at least 2 months). Due to restrictions in ordering HbA1C, we have defined the "initial HbA1C" as one obtained within the six weeks preceding, or following the initial visit to MDLUC.

In this study, the exposure is categorized in two ways. First, patients are assigned to either a "high" or "low" group with the cut off of 8.0. Second, patients are assigned to either "high", "intermediate" or "low" HbA1C with cut offs at 6.5 and 11.   This is shown in figure 3.

Figure 3   Distribution of Patients by Cohort (two separate analyses)
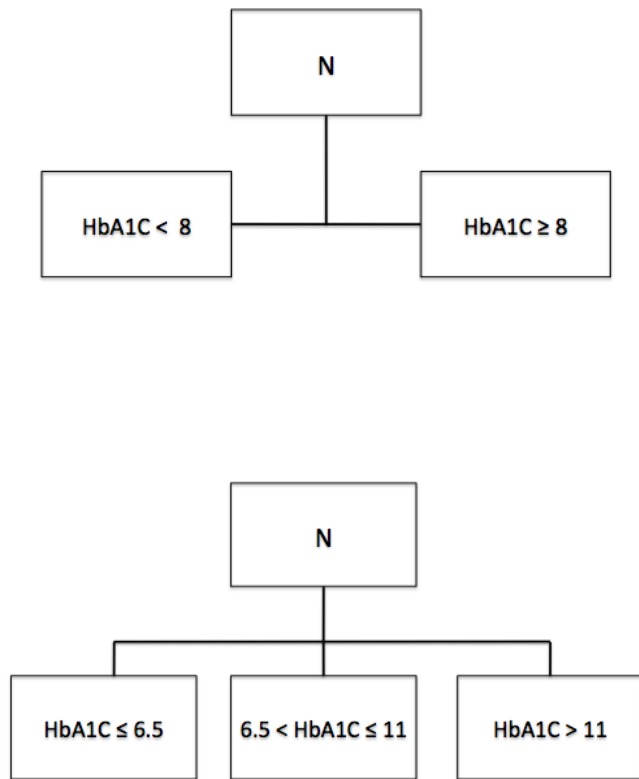
The duration of follow-up for this study is 6 months or a maximum of 6 months. Those patients who have not healed their DFU at a six month follow-up are considered as "not-healed." This cutoff was selected based on the mean time to healing of a DFU and study feasibility. Furthermore, it is relatively common in clinical practice to consider a DFU to be "futile" if no healing has occurred over a 6-month period.

The outcome of interest in this study is ulcer healing. For the purposes of this study, an ulcer is considered to be healed when there is epithelial tissue overlying the area of previous ulceration or, stated another way, the wound is "closed". If the area immediately deep to the newly epithelialized region has necrotic tissue or a purulent collection than this wound is not considered to be 'closed'. For example, epithelialization over an abscess would not be considered "healed" as the usual immediate response would be to incise this tissue to allow the deep collection to be removed. Ultimately, when a clinician determined the ulcer to be healed, the patient was discharged from MDLUC.

This study was completed as a dynamic cohort. Patients were recruited both retrospectively and prospectively. The clinic had been running for several months at the onset of the study and those patients who had previously been seen in the clinic had their charts reviewed retrospectively. Patients who were enrolled prospectively and provided HRQOL outcome measures signed informed consent consistent with REB approval. Those patients included in the retrospective review, did not provide individual consent. This is standard for retrospective case reviews approved through Dalhousie University and in-keeping with the Tri-Council policy statement of ethical conduct for research involving humans.

4.2.2   Inclusion and Exclusion Criteria

Patients who met the following criteria were included in this study:

- Attended the MDLUC clinic with a DFU
- Able to provide informed consent (age & capacity)
- Able to read, write and understand English
- A "DFU" by definition:
    - Diagnosis of DM
    - Delayed healing (>14 days)
    - Ulcer below the malleoli

Patients were excluded if they did not meet the above criteria, or:

- Were too sick/unwell/frail for continued follow-up on an outpatient basis

To clarify, we considered a diabetic foot ulcer to be a complication of diabetes mellitus. Patients required a previous diagnosis of DM to be considered. An ulceration was considered to be any wound on the foot that had evidence of delayed healing >14 days. There were no restrictions on the cause(s) or mechanism(s) of the original injury (for example trauma, pressure – external or internal, or other). We have accepted that DFUs have as a commonality a peripheral neuropathy. Patients who met all of the above criteria but had lesions above the level of the malleoli were excluded as this site of ulceration is most attributable to isolated vascular pathology.   Finally, patients were excluded if they were too sick, unwell or frail for ongoing and regular outpatient treatment. Patients who required a brief hospitalization for therapy (commonly intravenous antibiotics or surgical treatment) were not excluded from the study if, after the hospitalization, they were followed through MDLUC.

4.2.3 Research Ethics Board Approval

Research Ethics Board Approval was obtained from the Capital Health Research Ethics Board at the Centre for Clinical Research. Full approval was obtained as of October 4th, 2013 and this was assigned REB FILE #: CDHA-RS/2014-125.

4.2.4 Patient Recruitment

Patients were enrolled into this study both prospectively and retrospectively.

Retrospective: Patients seen in the MDLUC prior to study onset were enrolled retrospectively. A complete list of patients who had been seen in the MDLUC was obtained through scheduling software (STAR & PHS). A limited review of patient records was completed for each of these patients to determine whether or not they were eligible to be included into this study. Those patients who met inclusion criteria had complete review of their visits to the MDLUC clinic as well as all investigations, treatments and consultations pertaining to the DFU. Some of the retrospectively identified patients were still undergoing care in MDLUC at study onset and were followed prospectively for wound healing.

Prospective: A small number of patients were included in the prospective portion of the study. These patients were identified as candidates for the study

from MDLUC patient lists on clinic days and were approached by the research associate who invited them to take part in the study. Patients were only approached once they had been placed in the private examination room. Furthermore, patients were reminded that participation was entirely voluntary and their willingness or lack thereof to participate would in no way change the clinical care they received. Patients who were willing to be included in the study, provided informed consent for their participation in the study.

Patients, regardless of prospective or retrospective enrollment, were followed to ulcer healing or a maximum of 6 months (whichever occurred first). The timeline of patient recruitment and follow-up is represented graphically in Figures 4 and 5.

Figure 4   A schematic representation of the timeline of patient recruitment and follow-up of several patients over the calendar year.
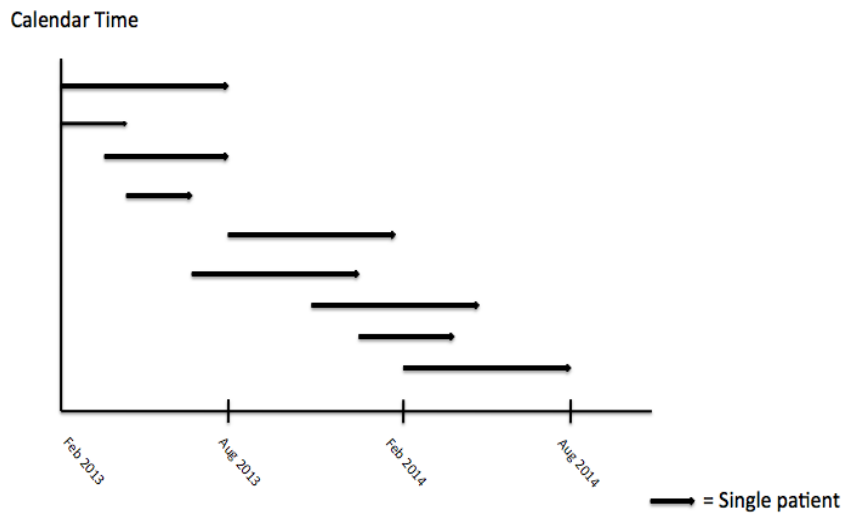
Figure 5   A schematic representation of the timeline of patient recruitment and
               follow-up of several patients as described in scientific time.

Scientific Time

0 Months
-Initial visit care
pathway
-HRQOL
-HbA1C

2 Months
-Follow-up visit
care pathway
-HRQOL

4 Months
-Follow-up visit
care pathway
-HRQOL

6 Months
-Follow-up visit
care pathway
-HRQOL

= Single patient
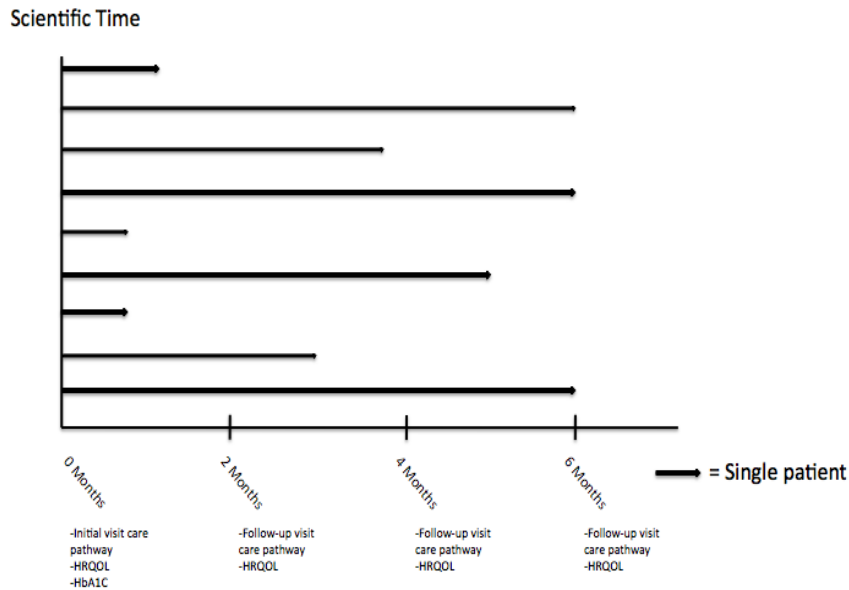
4.2.5   Data collection

       At the initial visit to the MDLUC, the CNS completed an initial assessment

using the MDLUC Initial Assessment Tool (Appendix B). This tool was developed as

an evidence-based clinical care pathway to collect clinically relevant information

and to identify the potential detriments to healing a DFU as well as to initiate

relevant investigations and treatments for each. The MDLUC Initial Assessment

Tool captured the severity of the ulcer through the Strauss classification.   The most

recent HbA1C was reviewed by the CNS and documented on the Initial Assessment

Tool. If an updated HbA1C was not available through the electronic medical record or from the referring physician, the CNS ordered it.

Subsequent visits for each patient were scheduled based on clinical need. The CNS employed the MDLUC Follow-up Assessment Tool at each sequential visit. If the HbA1C was ordered on the initial visit, than this was captured on the first return visit. Changes to each of the detriments to healing a DFU were captured as part of the clinical pathway. A complete list and description of all data points collected, source and type of data obtained is included in Appendix D.

The data at each visit was collected by the CNS and recorded on either the "Initial visit" or "follow-up visit" tool. These clinical pathways were scanned into the electronic patient record. The original copy was sent to patient health records and handled in the standard manner. The primary author accessed the scanned documents through the hospital's electronic medical record and entered the relevant data points into a spreadsheet. Patients were assigned a unique and de-identified study ID. The master spreadsheet was secured on a password-protected computer in a locked research office. When it was necessary to transmit portions of the master spreadsheet via electronic or portable storage means, a unique password was applied to the file. The research assistant verified data points.

4.2.6   Sample Size Calculation

A standard sample size calculation requires a known value for the level of significance, power, effect size and standard deviation in the population. The effect size of HbA1C was not able to be determined from the literature. As such, we were unable to complete a simple calculation for the sample size and therefore required computer modeling software.

Information on the mean and median times of DFU healing as well as the distribution of data was obtained from a paper by Ince et al [6]. This study reported a median healing time of a DFU to be 63 days (range 18-1486 days) of which 59.3% of the ulcers were healed by week 12, 70.5% by 20 weeks, and 86.6% by 52 weeks for a total sample of 376 ulcers. HbA1C was shown to have a normal distribution with a mean value of 8.1 and a standard deviation of 1.3.

Using modeling software, a parametric distribution of the gamma distribution family with parameters shape 0.63 and scale 200, matched Ince's distribution of the data. A medium effect size of 0.30 was tested using Monte-Carlo simulation methodology using a Cox proportional hazard regression model with time to healing as the primary outcome and HbA1C as the explanatory variable. Censoring of the data was at a 6-month period given the nature of the study. Based on 10,000 simulations a sample size of 130 ulcers was calculated to provide over 80% power at alpha 0.05 to detect an effect size of 0.30, which translates into a

hazard ratio of 1.24. This model did not control for potential confounders. The

simulation code in R Statistical Software and the results from simulation for sample

size calculation are presented in Appendix E.

4.2.7   Statistical Analysis

Data was analyzed using SPSS Statistics software (SPSS, Chicago, IL). Incident

rates of the outcome (ulcer healing) were calculated between the various exposure

groups in two ways: first - Low (HbA1C <8.0) and High (HbA1C ≥ 8.0); second – Low

(HbA1C ≤ 6.5), Intermediate (6.5 <HbA1C ≤ 11.0) and High (HbA1C >11.0). We

provided descriptive data for patient demographics including age, sex, duration of

ulcer (months), location of ulcer in the axial plane (plantar, dorsal), location of ulcer

in the coronal plane (forefoot, midfoot, hindfoot) and the Strauss score. Where the

independent variable (HbA1C) was categorized as High vs. Low, a Wilcoxen signed

rank test was used to determine if there were statistically significant differences

between the groups for age, duration of ulcer and Strauss score. This was used as an

alternative to the t-test as the data failed tests for normalcy. Where the independent

variable (HbA1C) was categorized as High, Intermediate or Low, a Kruskal-Wallace

H test was used to determine if there were statistically significant differences

between the groups for age, duration of ulcer and Strauss score. As was the case

with the previous statistical analysis, an alternative to an ANOVA test was employed

as the data failed tests for normalcy. A Chi-squared test was used to detect

differences between sex and location of ulcer in both analyses.

Time to healing of the ulcer was analyzed with a Kaplan Meier survival analysis. This was repeated for both ways of categorizing the exposure (HbA1C). Patients lost to follow-up were included in the survival analysis – censored for the last known visit at which the ulcer was open. A logistic regression was employed to determine if age, sex, ulcer severity (measured via Strauss score), changes to three detriments to healing (vascular supply, infection and offloading) had an effect on ulcer healing by category of HbA1C. Changes to the detriment to healing was categorized for the calculation. Those detriments to healing which were optimized at the start of the study interval were assigned a value of "0", those detriments which were not optimized at the onset of the study but which were optimized during the course of treatment were assigned "1" and those detriments which remained not optimized were assigned "2". We calculated and reported an odds ratio and 95% CI for each variable. A proportional hazards regression analysis (Cox model) was also employed for each of the variables described above. The detriments to healing were treated in the same manner as in the logistic regression model. Finally, a regression model was used to analyze HbA1C as a continuous variable to determine if an effect size could be quantified for each incremental increase in HbA1C value. For both the logistic regression and the cox regression analysis cases with missing data were omitted from the calculations.

4.2.8   Potential Confounders

The potential confounders in this study include: poor nutrition, smoking, plantar pressure, deformity, infection and poor vascular supply. Examination of the confounders in this study was of critical importance. We considered all of the potential detriments to healing as having the ability to play a role in the delayed healing of a DFU (and therefore to act as a confounder) but infection and poor vascular pathology were identified in the causal pathway (Figure 2) as potentially having a direct effect on glycemic control and wound healing.

The presence or absence of each of the potential confounders was captured and recorded with the intake and follow-up clinical pathways that were employed at each visit. However, there were challenges in completing this evaluation, as some of it was simply not captured in the patient record. Those detriments to healing that we were unable to determine change in during the course of the study were: poor nutrition, smoking status, and deformity. In contrast, we were able to capture changes in the following detriments to healing: offloading, infection, and vascular pathology. Conveniently, infection and vascular pathology were likely to have (from the literature) the greatest risk of having an effect on glycemic control and the healing of a DFU. The presence or absence of the detriment to healing as well as the interval change over the study period was considered in the data analysis and assessed with a proportional hazards regression analysis (Cox model).

4.2.9   Bias

In this study there are several potential sources of bias. With respect to selection bias, both recruitment and loss-to-follow-up (LTF) are areas of concern. Recruitment of patients took place in a consecutive manner. We had anticipated requiring a comparison to be made between those recruited and those patients who declined enrollment to ensure that there were no significant demographical differences between the two groups. However this was not necessary due to the fact that most patients were captured in the retrospective review. Losses to follow-up were minimal (total =5), likely due to the fact that the study was closely related to clinical care. We attempted to contact all patients who are lost to follow-up in order to determine the cause and their outcome.

Potential sources of information or classification bias in this study may stem from an inability to blind assessors and the potential for patients to move between exposure categories. The inability to blind assessors (in particular the Clinical Nurse Specialist who will be obtaining the data) will be identified in the reporting of the study results. The possibility of patients moving between exposure categories is in effect the nature of the study. It is conceivable that a patient who presents to the clinic with a given HbA1C value may have experience a change in HbA1C over the study period. This change in glucose control can be seen when a deep infection develops, when medications are changed or when a number of other scenarios occur.   However, the exposure of interest was that of the HbA1C at time of

presentation, if there is a significant change in the HbA1C during the treatment interval, this may be of relevance but is outside the scope of the current study.

4.3 RESULTS

4.3.1   Patient Recruitment

A total of 225 ulcers were reviewed at the MDLUC during the study period. Of these, 76 were in patients without diabetes and 26 did not meet inclusion criteria (e.g. ulcer above the level of the malleoli or non-delayed healing). A total of 123 ulcers met inclusion criteria. Of these, 4 did not obtain a HbA1C during the specified period and 6 were lost to follow-up prior to 6 months or documented healing of the ulcer.   9 patients underwent an amputation prior to 6 months of treatment at MDLUC.

A diagram of the patient flow is illustrated in Figure 6.

Figure 6   Patient flow
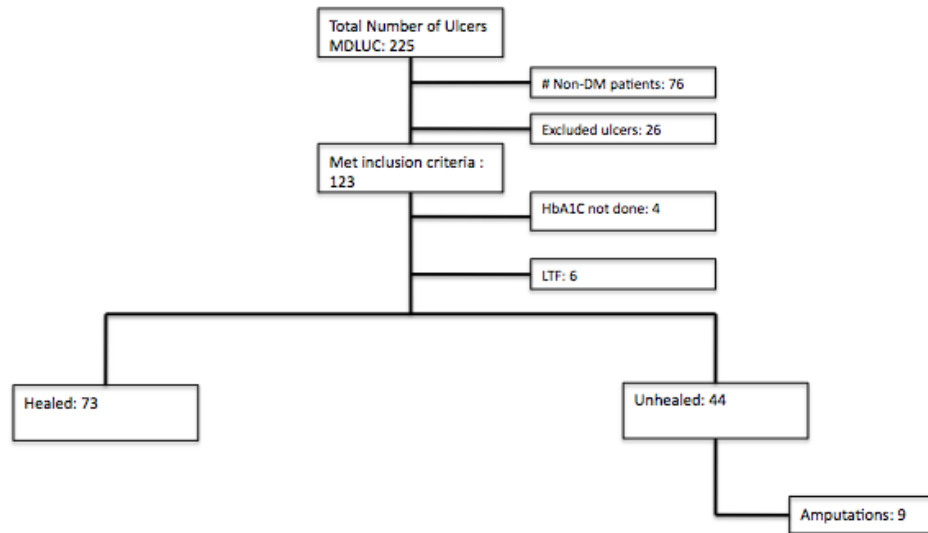
The patients were then classified by exposure two ways: first, as either

a"high" or "low" HbA1C and secondly as either "high", "intermediate" or "low"

HbA1c. As stated previously, 4 out of the 123 patients did not have a recorded

HbA1C value within 6 weeks of presentation to MDLUC. However, a HbA1C was

available for all 4 patients outside of this window. The HbA1C identified outside the

window ranged from 7.6 -9.0 for all 4 patients and was within a maximum of 5

months from presentation of a DFU. We estimated that the likelihood of a

substantial change of HbA1C over this timeframe would be small. Therefore, we

accepted that we could classify all four of these patients in the "intermediate"

category where our exposure was classified as high, intermediate or low. We

excluded all 4 patients from the analysis whereby the exposure was classified as

high or low as all of the values were within 1 point from the cutoff.   The sample size

was therefore different for the two ways to analyze the exposure.   This is described

in Figure 7 and 8.

Figure 7   Ulcer distribution where exposure (HbA1C) was designated as either
                  "Low" or "High"
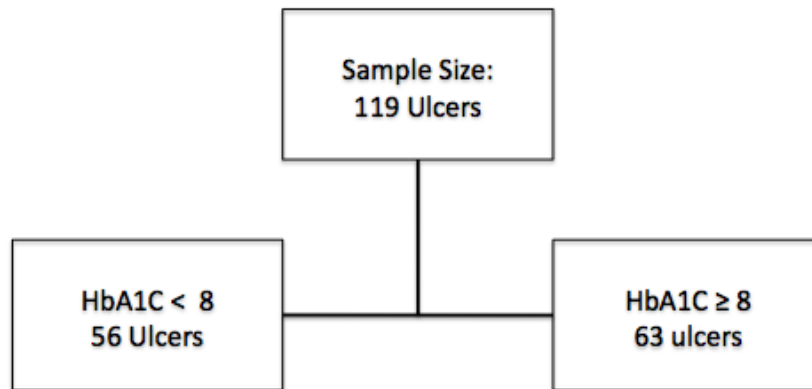
Figure 8   Ulcer distribution where exposure (HbA1C) was designated as either
                "Low", "Intermediate" or "High"
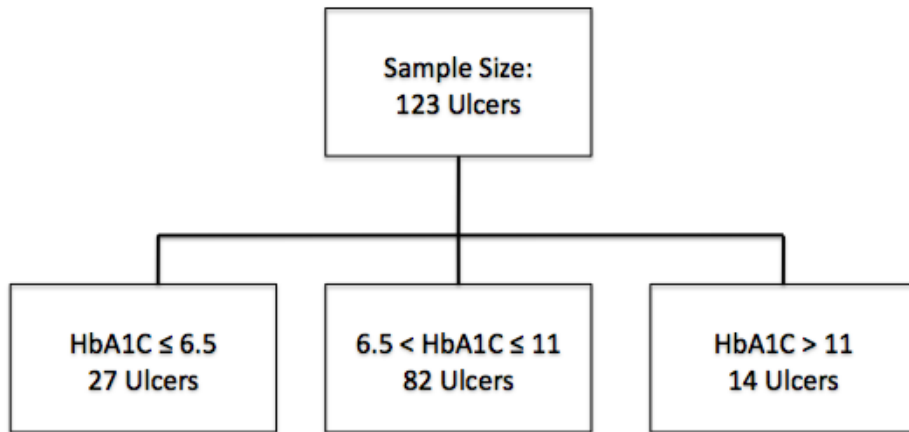
4.3.2   Patient Characteristics

        Table 3 outlines the patient characteristics when patients are categorized as

having a "high" or a "low" HbA1C. Statistically significant differences are noted for

age (p=0.001) and Strauss score (p=0.011). The Strauss score is a measure of ulcer

severity where a lower score indicates a more severe ulcer [4].

Table 3   Patient characteristics by HbA1C (either "low" or "high")

Demographics	HbA1C		P-value
	<8 (N=56)	≥8 (N=63)	
Age (yrs)	65	57	0.001
Sex (% Male)	0.76	0.75	0.368
Duration of Ulcer (mos)	6.8	8.1	0.620
Location of Ulcer (%)			
Dorsal	7	11	0.751
Plantar	93	89	
Hindfoot	15	8	0.538
Midfoot	22	22	
Forefoot	63	70	
Strauss Score	6.9	8.1	0.011

When patients are classified by HbA1C as "high," "intermediate," or "low" (Table 4), the only statistically significant difference between the groups is age (p=0.02). Patients with a higher HbA1C are younger than those with a low or intermediate level.

Table 4   Patient characteristics by HbA1C ("low", "intermediate" and "high")

Demographics	HbA1C			
	≤6.5 (N=27)	6.5<HbA1C≤11 (N=82)	>11 (N=14)	P-value
Age (yrs)	65	60	54	0.024
Sex (% Male)	0.74	0.74	0.57	0.276
Duration of Ulcer (months)	7.6	6	14	0.154
Location of Ulcer (%)				
Dorsal	15	7	20	0.634
Plantar	85	93	80	
Hindfoot	8	12	13	0.390
Midfoot	12	26	20	
Forefoot	80	62	67	
Strauss Score	7.3	7.6	7.9	0.76

4.3.3   Ulcer Healing

In the analysis which divided patients into either a "high" HbA1C or "low" HbA1C a total of 35 of the 61 (57%) patients healed at a mean time of 3.1 months in the "high" group in comparison to 29 of 52 (56%) at a mean time of 2.0 months in the "low" group.

In the second analysis whereby patients were divided into either a "high", "intermediate" or "low" HbA1C a total of 10 out of the 14 (71%) patients healed at a mean time of 3.4 months in the "high" group in comparison to 41 out of 79 (52%) at

a mean time of 2.6 months in the 'intermediate group" and 14 out 24 (58%) of the

ulcers healed in the "low" group at a mean time of 2.1 months.

A Kaplan-Meier estimate is a standard nonparametric estimator of the

survival function. In this study, we selected the inverse (1-survival) or cumulative

incidence curve to analyze the healing of DFUs by category of HbA1C. The

cumulative incidence curves are shown in Figures 9 and 10.   No significant

difference was found between the survival curves in either analysis.

Figure 9   Kaplan-Meier Survival Curve (shown as 1-KM) for Ulcer Healing (in
                percentage) by Categorization of HbA1C (Low and High) in Time
                (months)
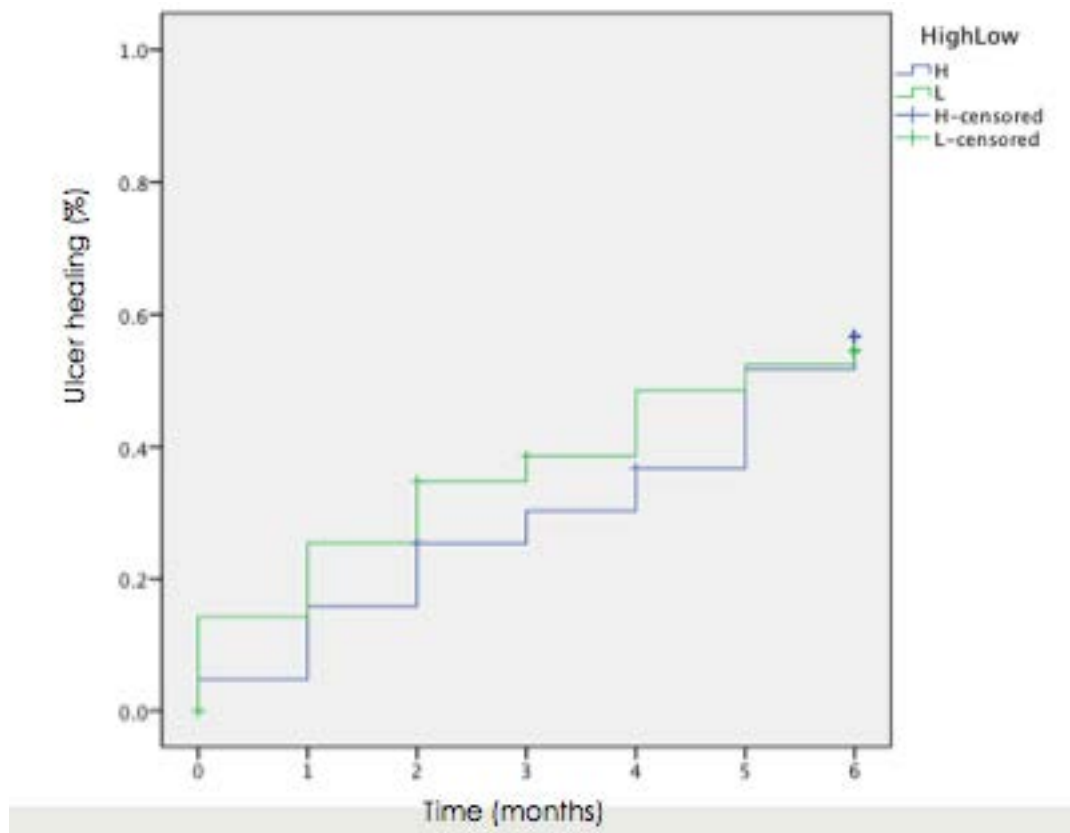
Figure 10   Kaplan-Meier Survival Curve (shown as 1-KM) for Ulcer Healing (in percentage) by Categorization of HbA1C (Low and High) in Time (months)
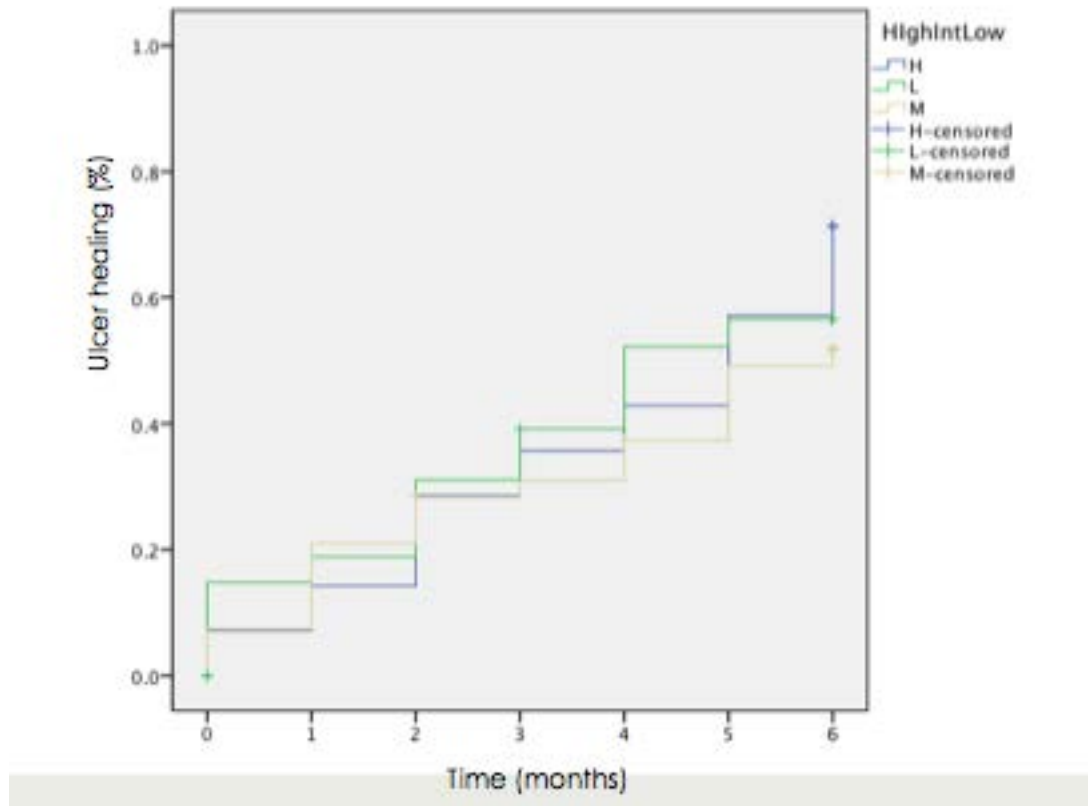
4.3.4 Detriments to healing a DFU

Table 5 and 6 describe the state of the detriments to healing over the study period. Recorded in these tables is the total number of patients where the detriment to healing was already optimized at the initial visit, the total number of patients that was not initially optimized but were optimized over the treatment period at MDLUC, and the total number that never achieved optimization of the detriment. One striking feature exists with regards to the confounders. Near

uniform care was provided to the patients. All of the patients who presented with

evidence of infection at the time of the initial visit were treated and optimized by the

final visit. Of the 88 patients who presented without previous treatment of plantar

offloading only 8 were not optimized by the final visit. The same is true of vascular

supply, however of those patients who presented without optimization of this

detriment, only a very small number underwent an intervention to reverse this.

Table 5   Total number of patients where the detriment to healing was optimized at the initial visit ("Optimized Initial"), optimized over the study period ("Subseq. Optimized") and Not Optimized at final visit ("Not Optimized") by categorization of HbA1C as either "high" or "low"

Detriments to Healing	HbA1C					
	<8 (N=56)			≥8 (N=63)		
	Optimized Initial	Subseq. Optimized	Not Optimized	Optimized Initial	Subseq. Optimized	Not Optimized
Vascular Supply	34	4	16	44	3	7
Infection	49	7	0	47	16	0
Offloading	14	32	2	15	38	4

Table 6   Total number of patients where the detriment to healing was optimized at the initial visit, subsequently optimized over the study period, and not optimized at final visit by categorization of HbA1C as either "high," "intermediate," or "low"

Detriments to Healing	HbA1C								
	≤ 6.5 (N=27)			6.5<HbA1C≤11 (N=76)			> 11 (N=14)		
	Opt Ini	Subs Opt	Not Opt	Opt Ini	Subs Opt	Not Opt	Opt Ini	Subs Opt	Not Opt
Vascular Supply	16	0	9	57	6	12	8	1	3
Infection	23	4	0	66	16	0	10	3	0
Offloading	5	17	1	20	48	0	4	7	0

*Opt Ini = Optimized Initial; Sub Opt = Subsequently Optimized; Not Opt = Not Optimized

4.3.5 Logistic Regression

A logistic regression analysis was employed to run a model predicting the outcome healing using HbA1C, sex, age, Strauss score as well as the following detriments to healing: infection, vascular supply and offloading. The results are summarized in Table 7. Appendix F includes the categorical variable coding and model summary for this analysis. The results do not show a statistically significant odds ratio (OR) for any of the variables in the model. The 95% CI for the OR crosses 1 for all variables.

Table 7   Logistic Regression Analysis

Variable	Odds Ratio (OR)	95% CI for OR	
		Upper	Lower
HbA1C	0.858	0.653	1.127
Sex	1.76	0.598	5.182
Age (60)	0.634	0.392	1.024
Strauss Score	1.040	0.831	1.303
Infection (Subseq. Optimized)	1.678	0.416	6.766
Vascular Supply (Subseq Optimized)	0.323	0.051	2.049
Vascular Supply (Not Optimized)	0.623	0.199	1.946
Offloading (Subseq Optimized)	0.846	0.366	1.953

4.3.6 Cox Regression

Cox regression analysis was performed for both ways of categorizing HbA1C.

In both models a Hazard Ration (HR) as well as 95% CI for HR was reported and

summarized in Table 8 and 9. Appendix G includes the categorical variable coding

and model summary for this analysis. Neither analysis demonstrated a statistically

significant Hazard Ratio for any of the variables. All variables had 95% CI for the HR

which crossed 1.

Table 8   Cox Regression for categorization of HbA1C as "low" or "high"

Variable	Hazard Ratio (HR)	95% CI for HR	
		Upper	Lower
HbA1C (high)	0.809	0.458	1.429
Sex	0.929	0.729	1.185
Age (60)	0.817	0.446	1.497
Strauss Score	1.061	0.516	2.182
Infection (Subseq. Optimized)	0.400	0.095	1.679
Vascular Supply (Subseq Optimized)	0.689	0.336	1.453
Vascular Supply (Not Optimized)	1.117	0.625	1.997
Offloading (Subseq Optimized)	0.492	0.109	2.264

Table 9   Cox Regression for categorization of HbA1C as "low," "intermediate," or "high"

Variable	Hazard Ratio (HR)	95% CI for HR	
		Upper	Lower
HbA1C (Int)	0.886	0.446	1.758
HbA1C (High)	1.125	0.437	2.896
Sex	0.932	0.732	1.186
Age (60)	0.850	0.463	1.560
Strauss Score	1.129	0.565	2.256
Infection (Subseq. Optimized)	0.428	0.102	1.800
Vascular Supply (Subseq Optimized)	0.710	0.344	1.465
Vascular Supply (Not Optimized)	1.055	0.591	1.882
Offloading (Subseq Optimized)	0.555	0.155	1.934

A final Cox regression analysis was performed using HbA1C as a continuous variable (Table 10). The categorization of the remaining variables for this model was identical to the Cox Regression analysis above.   This produced a statistically

significant HR for HbA1C (HR=0.823, 95% CI 0.68-0.996). Which suggests an

increased time to healing for each 1 point increase in HbA1C.

Table 10   Cox Regression for HbA1C as a continuous variable

Variable	Hazard Ratio (HR)	95% CI for HR	
		Upper	Lower
HbA1C	0.823	0.68	0.996
Sex	1.486	0.735	3.008
Age (60)	0.727	0.519	1.020
Strauss Score	1.016	0.862	1.197
Infection (Subseq. Optimized)	1.303	0.520	3.285
Vascular Supply (Subseq Optimized)	0.429	0.917	1.897
Vascular Supply (Not Optimized)	0.652	0.289	1.472
Offloading (Subseq Optimized)	0.921	0.498	1.706
Offloading (Not Optimized)	0.378	0.46	3.074

4.3.7 Amputations

Overall, 9 amputations occurred during the study interval. The cause of

amputation for 6 cases was a necrotic or gangrenous toe. Three patients elected

amputation prior to six months of treatment at the MDLUC clinic. The mean time to

amputation was 5.3 months. No differences were found in terms of duration of ulcer

or detriments to healing present for those ulcers which resulted in amputation.

Patient distribution occurred as follows: 6 were "high" HbA1C and 2 were "low"

HbA1C for the high/low analysis and 2 were "high" HbA1c, 5 were "intermediate"

HbA1C and 1 was "low" HbA1C for high/intermediate/low analysis. HbA1C was not

available for one patient that underwent an amputation.

The rate of amputation in this study was 7%.

4.4 INTERPRETATION

The research question for our project was a simple one: *Does poor glucose
control (elevated HbA1C) at time of presentation with a diabetic foot ulcer have an
impact on the time to heal an ulcer?* We have demonstrated with the background
information as well as the data analysis that there are many additional factors that
may contribute to the healing of a DFU. The additional factors include the potential
detriments to healing (poor nutrition, infection, smoking, vascular pathology,
plantar pressure and deformity) as well as patient characteristics (age, sex) and
ulcer characteristics (severity).

The survival analysis failed to show a significant difference between levels of
HbA1C and time to ulcer healing. Similarly, the logistic regression and Cox
regression analysis, for all but one model, failed to show a statistically significant
difference. The HR from this model would suggest an 18% increase in time to
healing for each 1-point increase in HbA1C, which represents a difference of
approximately 2 weeks. This model assumes a linear relationship between HbA1C
and healing. A quadratic model was also explored with this data and found to be

non-significant. The model that showed a difference between time to ulcer healing

and HbA1C should be interpreted with caution. This model included only cases with

complete data for the variables tested, as those with missing data were dropped

from the analysis (total N=90). The distribution of these cases by HbA1C is

demonstrated in Figure 11 and expressed by quintiles in Table 11.

Figure 11   Distribution of HbA1C values used in Regression Analysis Model
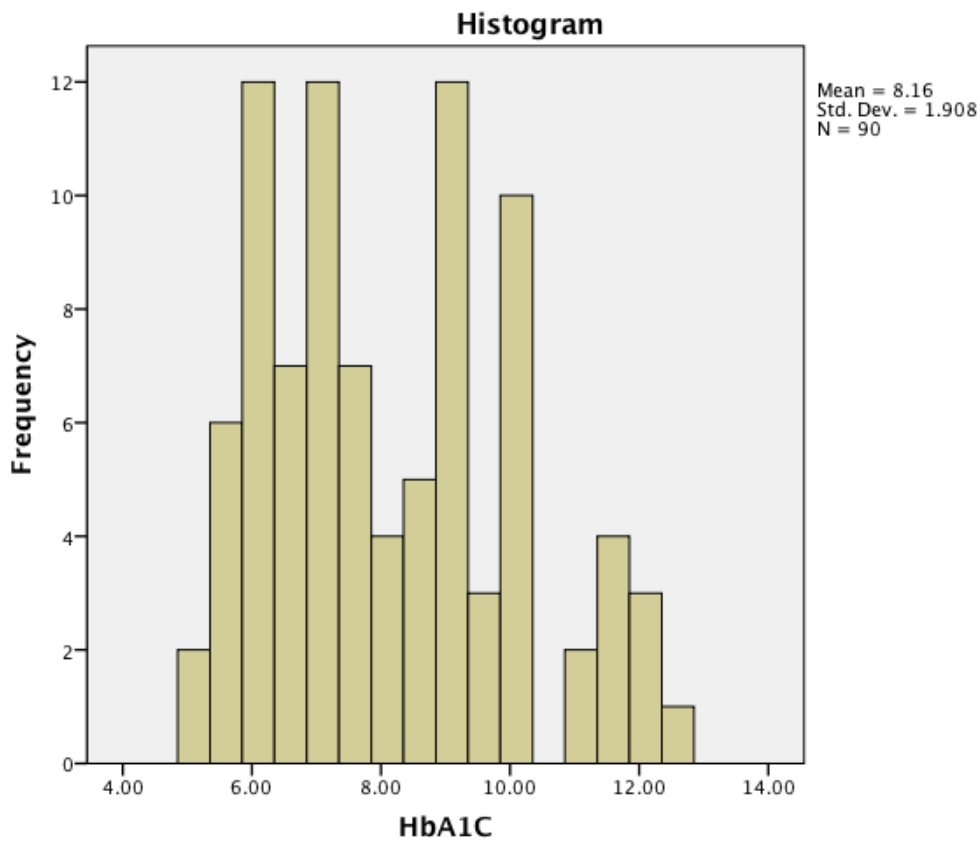
Table 11   Distribution of HbA1C values used in Regression Analysis by Quintiles

Quintiles of HbA1C (value distribution)	Number of cases
20 (5-1-6.19)	16
40 (6.2-7.09)	18
60 (7.1-8.75)	20
80 (8.76-9.8)	16
100 (9.9-12.5)	20

While this result is in keeping with our hypothesis, this study was not

powered to show this effect. We would suggest that this result should be considered

as a pilot for future research. To confirm if our findings are valid, the hypothesis

needs to be retested using HbA1C as a continuous variable, and accounting for the

potential interaction of age, sex as well as each of the detriments to healing with an

appropriately powered study.

We had expected to find statistically significant differences between

categories of HbA1C and time to healing in our survival analysis. This was not

found. There are several possible causes for this outcome. There is a chance that

the study we failed to recruit enough patients to detect the effect that differences in

HbA1C had on healing a DFU. The sample size calculated was 130 patients and we

recruited 123 ulcers. This could be conclusively ruled out as a possible cause for

our findings by recruiting 7 more patients. Unfortunately, this was not feasible with

the current recruitment strategy and time needed to complete this project. We did

not expect that there would be near uniform care with regards to the other detriments to healing. Our findings made it difficult to determine what (if any) role the confounders played in relation to HbA1C. It is possible that one of the detriments to healing which we did not capture well (e.g. smoking, nutrition or deformity) had a greater than expected influence on the outcomes.

Perhaps, the cutoff points used for the values of HbA1C were incorrect. The cutoffs tested in this study were taken from previous work, which demonstrated increased rates of complications for each of the thresholds we tested. However, these previously reported complications were not specifically healing of a DFU, but rather mortality and all-cause complications. Our data analysis suggests that a more accurate model may be the consideration of healing rates by HbA1C as a continuous variable.

Finally, there may be another time-point in the development and treatment of a DFU where the HbA1C is more predictive of outcome. Perhaps, a year prior to the onset of the DFU, or perhaps, the change in HbA1C over the study period may be more predictive. Again, further evaluation into these hypotheses is required.

The limitations of this study include a small sample size. This failed to allow us to account for the large number of potential confounders. The study design precluded the ability to blind either the assessors or the persons responsible for data analysis.

CHAPTER 5 CONCLUSIONS

The introduction outlined the severity and magnitude of the problem of

DFUs. It is simply put a problem of significant proportions for our country, for local

health-care organizations, for individual health-care providers as well as those

individuals with the condition.

Treating a DFU is difficult due to the multiple factors that may contribute to

the non-healing of an ulcer. We have proposed a novel causal pathway that

describes the potential interactions between the potential detriments to healing .

This pathway should be considered dynamic and is likely to change as further

research into DFUs continues. An additional interaction that could be placed onto

the pathways is between poor glucose control and deformity (due to Charcot

neuropathic arthropathy). The importance of this pathway is clear to both clinical

applications and future research.

We tested the hypothesis that poor glycemic control had a direct inhibitory effect on the healing of a diabetic foot ulcer. This potential detriment to healing was selected for its unique role in the pathophysiology of the disease, testability of the hypothesis and support in the literature. Our study, however, failed to uncover a direct relationship with poor glycemic control and the non-healing of a diabetic foot ulcer. Regression analysis of the role of optimizing infection, offloading, and vascular supply also failed to demonstrate significance.

The temptation might be to write off this lack of association and/or the concept of the detriments to healing a DFU. However, the most logical conclusion is that our study in fact, highlighted and demonstrated the concept that was initially presented – the study of a diabetic foot ulcer is a complex and multi-faceted topic.

Ultimately, any study, which fails to consider all of the potential detriments to healing of a DFU as well as the inter-relationships between the potential detriments, may be doomed to come up short.   A much larger study, which is powered to consider all of the confounders is necessary.

Further study should include an attempt to confirm and quantify the effect of the detriments to healing on both the healing of a DFU and on each other. Threshold values of HbA1C that are associated with a non-healing of DFU still need to be established. Alternatively it may be possible to describe a relationship between healing time and the incremental increase of HbA1C. Finally, other potential contributors to the non-healing of a DFU (beyond those proposed in this work) need to be investigated.

One need only spend a morning in a foot ulcer clinic to understand the significance and importance of this type of inquiry. The patients suffering with a DFU are deserving of improved treatment for this significant condition.

BIBLIOGRAPHY

1.   Association, C.D. *Diabetes: Canada at the Tipping Point*

2.   Dyck, R., *Epidemiology of Diabetes Mellitus among First Nations and Non-First Nations Adults.* Can Med Assoc J, 2010. **182**: p. 249-256.

3.   Nations, A.o.F., *First Nations Longitudinal Health Survey 2002-2003.* p. 71.

4.   Strauss, M.B. and I.V. Aksenov, *Evaluation of Diabetic Wound Classifications and a New Wound Score.* Clinical Orthopaedics and Related Research, 2005. **439**: p. 79-86.

5.   Foundation, I.D. *2012: IDF Diabetes Atlas.* 2012.

6.   Ince, P., F.L. Game, and W.J. Jeffcoate, *Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area.* Diabetes Care, 2007. **30**(3): p. 660-3.

7.   Mann, R.A., N.K. Poppen, and M. O'Konski, *Amputation of the great toe. A clinical and biomechanical study.* Clin Orthop Relat Res, 1988(226): p. 192-205.

8.   Landry, G.J., et al., *Predictors of healing and functional outcome following transmetatarsal amputations.* Arch Surg, 2011. **146**(9): p. 1005-9.

9.   Hosch, J., et al., *Outcomes of transmetatarsal amputations in patients with diabetes mellitus.* J Foot Ankle Surg, 1997. **36**(6): p. 430-4.

10.   Dormandy, J., L. Heeck, and S. Vig, *Major amputations: clinical patterns and predictors.* Semin Vasc Surg, 1999. **12**(2): p. 154-61.

11.   Larsson, J., et al., *Long-term prognosis after healed amputation in patients with diabetes.* Clin Orthop Relat Res, 1998(350): p. 149-58.

12.	Brazier, J.E., et al., *Validating the SF-36 health survey questionnaire: new outcome measure for primary care.* BMJ, 1992. **305**(6846): p. 160-4.

13.	Alonso, J., et al., *Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project.* Qual Life Res, 2004. **13**(2): p. 283-98.

14.	Ware, J.E., Jr., et al., *Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems. Results from the Medical Outcomes Study.* JAMA, 1996. **276**(13): p. 1039-47.

15.	Glasgow, R.E., et al., *Quality of life and associated characteristics in a large national sample of adults with diabetes.* Diabetes Care, 1997. **20**(4): p. 562-7.

16.	Rubin, R.R. and M. Peyrot, *Quality of life and diabetes.* Diabetes Metab Res Rev, 1999. **15**(3): p. 205-18.

17.	Ribu, L., et al., *A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population.* Qual Life Res, 2007. **16**(2): p. 179-89.

18.	Goodridge, D., et al., *Quality of life of adults with unhealed and healed diabetic foot ulcers.* Foot Ankle Int, 2006. **27**(4): p. 274-80.

19.	Gandek, B., et al., *Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment.* J Clin Epidemiol, 1998. **51**(11): p. 1171-8.

20.	Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.

21. Hopman, W.M., et al., *Canadian normative data for the SF-36 health survey. Canadian Multicentre Osteoporosis Study Research Group.* CMAJ, 2000. **163**(3): p. 265-71.

22. Ware, J.E., M. Kosinski, and S.D. Keller, *SF-12: How to score the SF-12 Physical and Mental Health Summary Scales.* 3 ed. 1998: Quality Metric Inc, Lincoln, RI.

23. Jaksa, P.J. and J.L. Mahoney, *Quality of life in patients with diabetic foot ulcers: validation of the Cardiff Wound Impact Schedule in a Canadian population.* Int Wound J, 2010. **7**(6): p. 502-7.

24. Piaggesi, A., et al., *Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial.* Diabet Med, 1998. **15**(5): p. 412-7.

25. Katz, I.A., et al., *A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers.* Diabetes Care, 2005. **28**(3): p. 555-9.

26. Wright, J.G., M.F. Swiontkowski, and J.D. Heckman, *Introducing levels of evidence to the journal.* J Bone Joint Surg Am, 2003. **85-A**(1): p. 1-3.

27. Wright, J.G., T.A. Einhorn, and J.D. Heckman, *Grades of recommendation.* J Bone Joint Surg Am, 2005. **87**(9): p. 1909-10.

28. Nordin, M. and V. Frankel, *Basic Biomechanics of the Musculoskeletal System.* 3rd ed. 2001: Lippincott Williams & Wilkins, Baltimore, Maryland. 467.

29. Batista, F., et al., *Minimally invasive surgery for diabetic plantar foot ulcerations.* Diabet Foot Ankle, 2011. **2**.

30. Chen, L. and J. Greisberg, *Achilles lengthening procedures.* Foot Ankle Clin, 2009. **14**(4): p. 627-37.

31. Clark, G.D., E. Lui, and K.D. Cook, *Tendon balancing in pedal amputations.* Clin Podiatr Med Surg, 2005. **22**(3): p. 447-67.

32. Colen, L.B., et al., *Achilles tendon lengthening: friend or foe in the diabetic foot?* Plast Reconstr Surg, 2013. **131**(1): p. 37e-43e.

33. Greenhagen, R.M., A.R. Johnson, and N.J. Bevilacqua, *Gastrocnemius recession or tendo-achilles lengthening for equinus deformity in the diabetic foot?* Clin Podiatr Med Surg, 2012. **29**(3): p. 413-24.

34. Hastings, M.K., et al., *Effects of a tendo-Achilles lengthening procedure on muscle function and gait characteristics in a patient with diabetes mellitus.* J Orthop Sports Phys Ther, 2000. **30**(2): p. 85-90.

35. Holstein, P., et al., *Achilles tendon lengthening, the panacea for plantar forefoot ulceration?* Diabetes Metab Res Rev, 2004. **20 Suppl 1**: p. S37-40.

36. Kaspar, S.S., *Effect of Achilles tendon lengthening on neuropathic plantar ulcers.* J Bone Joint Surg Am, 2004. **86-A**(4): p. 870; author reply 870-1.

37. La Fontaine, J., et al., *New and recurrent ulcerations after percutaneous achilles tendon lengthening in transmetatarsal amputation.* J Foot Ankle Surg, 2008. **47**(3): p. 225-9.

38. Laborde, J.M., *Treatment of diabetic foot ulcers with tendon lengthening.* Am Fam Physician, 2009. **80**(12): p. 1351; author reply 1351.

39. Lin, S.S., T.H. Lee, and K.L. Wapner, *Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: the effect of tendo-Achilles lengthening and total contact casting.* Orthopedics, 1996. **19**(5): p. 465-75.

40. Mueller, M.J., et al., *Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial.* J Bone Joint Surg Am, 2003. **85-A**(8): p. 1436-45.

41. Nishimoto, G.S., C.E. Attinger, and P.S. Cooper, *Lengthening the Achilles tendon for the treatment of diabetic plantar forefoot ulceration.* Surg Clin North Am, 2003. **83**(3): p. 707-26.

42. Willrich, A., A.K. Angirasa, and R.A. Sage, *Percutaneous tendo Achillis lengthening to promote healing of diabetic plantar foot ulceration.* J Am Podiatr Med Assoc, 2005. **95**(3): p. 281-4.

43. Van De Weg, F.B., D.A. Van Der Windt, and A.C. Vahl, *Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration.* Prosthet Orthot Int, 2008. **32**(1): p. 3-11.

44. Thompson, P., et al., *Offloading diabetic foot ulcers.* Adv Skin Wound Care, 2006. **19**(1): p. 15-6, 19.

45. Tessler, S.L., *Total contact casting: an underused intervention.* Am Fam Physician, 1997. **55**(2): p. 425-6.

46. Spencer, S., *Pressure relieving interventions for preventing and treating diabetic foot ulcers.* Cochrane Database Syst Rev, 2000(3): p. CD002302.

47. Sinacore, D.R., *Total contact casting for diabetic neuropathic ulcers.* Phys Ther, 1996. **76**(3): p. 296-301.

48.   Rathur, H.M. and A.J. Boulton, *Pathogenesis of foot ulcers and the need for offloading.* Horm Metab Res, 2005. **37 Suppl 1**: p. 61-8.

49.   Piaggesi, A., et al., *An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast.* Diabetes Care, 2007. **30**(3): p. 586-90.

50.   Myerson, M., et al., *The total-contact cast for management of neuropathic plantar ulceration of the foot.* J Bone Joint Surg Am, 1992. **74**(2): p. 261-9.

51.   Mueller, M.J., *Application of plantar pressure assessment in footwear and insert design.* J Orthop Sports Phys Ther, 1999. **29**(12): p. 747-55.

52.   Morona, J.K., et al., *Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis.* Diabetes Metab Res Rev, 2013. **29**(3): p. 183-93.

53.   Malhotra, S., E. Bello, and S. Kominsky, *Diabetic foot ulcerations: biomechanics, charcot foot, and total contact cast.* Semin Vasc Surg, 2012. **25**(2): p. 66-9.

54.   Lavery, L.A., *Discussion: Off-loading the diabetic foot for ulcer prevention and healing.* Plast Reconstr Surg, 2011. **127 Suppl 1**: p. 257S-258S.

55.   Laing, P.W., D.I. Cogley, and L. Klenerman, *Neuropathic foot ulceration treated by total contact casts.* J Bone Joint Surg Br, 1992. **74**(1): p. 133-6.

56.   Laing, P., *Diabetic foot ulcers.* Am J Surg, 1994. **167**(1A): p. 31S-36S.

57.   Gutekunst, D.J., et al., *Removable cast walker boots yield greater forefoot off-loading than total contact casts.* Clin Biomech (Bristol, Avon), 2011. **26**(6): p. 649-54.

58.   Gray, M., *Is total contact casting effective for treating diabetic foot ulcers?* J Wound Ostomy Continence Nurs, 2006. **33**(4): p. 359-62.

59.   Ganguly, S., et al., *A comparative study between total contact casting and conventional dressings in the non-surgical management of diabetic plantar foot ulcers.* J Indian Med Assoc, 2008. **106**(4): p. 237-9, 244.

60.   Farid, K., M. Farid, and C.M. Andrews, *Total contact casting as part of an adaptive care approach: a case study.* Ostomy Wound Manage, 2008. **54**(6): p. 50-65.

61.   Faglia, E., et al., *Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial.* Diabetes Care, 2010. **33**(7): p. 1419-23.

62.   Conti, S.F., *Total contact casting.* Instr Course Lect, 1999. **48**: p. 305-15.

63.   Cavanagh, P.R. and S.A. Bus, *Off-loading the diabetic foot for ulcer prevention and healing.* Plast Reconstr Surg, 2011. **127 Suppl 1**: p. 248S-256S.

64.   Cavanagh, P.R. and S.A. Bus, *Off-loading the diabetic foot for ulcer prevention and healing.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 360-8.

65.   Cavanagh, P.R. and S.A. Bus, *Off-loading the diabetic foot for ulcer prevention and healing.* J Vasc Surg, 2010. **52**(3 Suppl): p. 37S-43S.

66.   Caravaggi, C., et al., *Nonwindowed nonremovable fiberglass off-loading cast versus removable pneumatic cast (AircastXP Diabetic Walker) in the treatment of neuropathic noninfected plantar ulcers: a randomized prospective trial.* Diabetes Care, 2007. **30**(10): p. 2577-8.

67.   Caputo, G.M., J.S. Ulbrecht, and P.R. Cavanagh, *The total contact cast: a method for treating neuropathic diabetic ulcers.* Am Fam Physician, 1997. **55**(2): p. 605-11, 615-6.

68.   Brem, H., et al., *Evidence-based protocol for diabetic foot ulcers.* Plast Reconstr Surg, 2006. **117**(7 Suppl): p. 193S-209S; discussion 210S-211S.

69.   Boulton, A.J., *The diabetic foot--an update.* Foot Ankle Surg, 2008. **14**(3): p. 120-4.

70.   Bentley, J. and A. Foster, *Management of the diabetic foot ulcer: exercising control.* Br J Community Nurs, 2008. **13**(3): p. S16, S18, S20 passim.

71.   Bell, R.A., et al., *Depressive symptoms and diabetes self-management among rural older adults.* Am J Health Behav, 2010. **34**(1): p. 36-44.

72.   Bell, D., *Evidence-based rationale for offloading treatment modalities.* Surg Technol Int, 2008. **17**: p. 113-7.

73.   Baker, R.E., *Total contact casting.* J Am Podiatr Med Assoc, 1995. **85**(3): p. 172-6.

74.   Armstrong, D.G., et al., *Off-loading the diabetic foot wound: a randomized clinical trial.* Diabetes Care, 2001. **24**(6): p. 1019-22.

75.   Armstrong, D.G., et al., *Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial.* Diabetes Care, 2005. **28**(3): p. 551-4.

76.   Armstrong, D.G. and K.A. Athanasiou, *The edge effect: how and why wounds grow in size and depth.* Clin Podiatr Med Surg, 1998. **15**(1): p. 105-8.

77.   Ali, R., et al., *Total contact cast for neuropathic diabetic foot ulcers.* J Coll Physicians Surg Pak, 2008. **18**(11): p. 695-8.

78.   Sibbald, G., et al., *Preparing the Wound Bed 2003: Focus on Infection and Inflammation.* Ostomy Wound Manage, 2003. **49**(11): p. 24-51.

79.   Lipsky, B.A., et al., *Diagnosis and treatment of diabetic foot infections.* Clin Infect Dis, 2004. **39**(7): p. 885-910.

80.   Armstrong, D.G., L.A. Lavery, and L.B. Harkless, *Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation.* Diabetes Care, 1998. **21**(5): p. 855-9.

81.   Armstrong, D.G. and B.A. Lipsky, *Diabetic foot infections: stepwise medical and surgical management.* Int Wound J, 2004. **1**(2): p. 123-32.

82.   Calhoun, J.H., et al., *Diabetic foot ulcers and infections: current concepts.* Adv Skin Wound Care, 2002. **15**(1): p. 31-42; quiz 44-5.

83.   Dos Santos, V.P., D.R. da Silveira, and R.A. Caffaro, *Risk factors for primary major amputation in diabetic patients.* Sao Paulo Med J, 2006. **124**(2): p. 66-70.

84.   Edmonds, M., *A natural history and framework for managing diabetic foot ulcers.* Br J Nurs, 2008. **17**(11): p. S20, S22, S24-9.

85. Edmonds, M., *Multidisciplinary care of the diabetic foot patient with infection.* Int J Low Extrem Wounds, 2010. **9**(1): p. 6-8.

86. Fisher, T.K., et al., *A stepwise approach for surgical management of diabetic foot infections.* J Am Podiatr Med Assoc, 2010. **100**(5): p. 401-5.

87. Frykberg, R.G., *Diabetic foot infections: evaluation and management.* Adv Wound Care, 1998. **11**(7): p. 329-31.

88. Frykberg, R.G., *A summary of guidelines for managing the diabetic foot.* Adv Skin Wound Care, 2005. **18**(4): p. 209-14.

89. Gardner, S.E. and R.A. Frantz, *Wound bioburden and infection-related complications in diabetic foot ulcers.* Biol Res Nurs, 2008. **10**(1): p. 44-53.

90. Gariani, K., I. Uckay, and B.A. Lipsky, *Managing diabetic foot infections: a review of the new guidelines.* Acta Chir Belg, 2014. **114**(1): p. 7-16.

91. Nagoba, B.S., et al., *A simple and effective approach for the treatment of diabetic foot ulcers with different Wagner grades.* Int Wound J, 2010. **7**(3): p. 153-8.

92. Xie, T., S. Lu, and R. Mani, *Diabetic foot infection in the world: - We need ways forward.* Int J Low Extrem Wounds, 2010. **9**(1): p. 3-5.

93. Younes, N.A. and F.G. Bakri, *Diabetic foot infection.* Saudi Med J, 2006. **27**(5): p. 596-603.

94. Zgonis, T. and T.S. Roukis, *A systematic approach to diabetic foot infections.* Adv Ther, 2005. **22**(3): p. 244-62.

95. Zgonis, T., et al., *Surgical management of diabetic foot infections and amputations.* AORN J, 2008. **87**(5): p. 935-46; quiz 947-50.

96. Gardner, S.E., et al., *The neuropathic diabetic foot ulcer microbiome is associated with clinical factors.* Diabetes, 2013. **62**(3): p. 923-30.

97. Arcavi, L. and N.L. Benowitz, *Cigarette smoking and infection.* Arch Intern Med, 2004. **164**(20): p. 2206-16.

98. Katona, P. and J. Katona-Apte, *The interaction between nutrition and infection.* Clin Infect Dis, 2008. **46**(10): p. 1582-8.

99. Vuorisalo, S., M. Venermo, and M. Lepantalo, *Treatment of diabetic foot ulcers.* J Cardiovasc Surg (Torino), 2009. **50**(3): p. 275-91.

100. Uccioli, L., *Advances in the treatment of peripheral vascular disease in diabetes and reduction of major amputations.* Int J Low Extrem Wounds, 2011. **10**(2): p. 72-4.

101. Soderstrom, M., et al., *Angiosome-targeted infrapopliteal endovascular revascularization for treatment of diabetic foot ulcers.* J Vasc Surg, 2013. **57**(2): p. 427-35.

102. Sigala, F., et al., *Transluminal angioplasty of isolated crural arterial lesions in diabetics with critical limb ischemia.* Vasa, 2005. **34**(3): p. 186-91.

103. Shojaiefard, A., et al., *Large and deep diabetic heel ulcers need not lead to amputation.* Foot Ankle Int, 2013. **34**(2): p. 215-21.

104. Setacci, C., et al., *Diabetic foot: surgical approach in emergency.* Int J Vasc Med, 2013. **2013**: p. 296169.

105. Scatena, A., et al., *Outcomes of three years of teamwork on critical limb ischemia in patients with diabetes and foot lesions.* Int J Low Extrem Wounds, 2012. **11**(2): p. 113-9.

106.   Ricco, J.B., et al., *Open surgery for chronic limb ischemia: a review.* J Cardiovasc Surg (Torino), 2013. **54**(6): p. 719-27.

107.   Peeters, P., et al., *Endovascular procedures and new insights in diabetic limb salvage.* J Cardiovasc Surg (Torino), 2012. **53**(1): p. 31-7.

108.   Mansilha, A. and D. Brandao, *Guidelines for treatment of patients with diabetes and infected ulcers.* J Cardiovasc Surg (Torino), 2013. **54**(1 Suppl 1): p. 193-200.

109.   Jeffcoate, W.J., et al., *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.* Health Technol Assess, 2009. **13**(54): p. 1-86, iii-iv.

110.   Hinchliffe, R.J., et al., *A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease.* Diabetes Metab Res Rev, 2012. **28 Suppl 1**: p. 179-217.

111.   Georgakarakos, E., et al., *Current achievements with topical negative pressure to improve wound healing in dehiscent ischemic stumps of diabetic patients: a case series.* Int J Low Extrem Wounds, 2013. **12**(2): p. 138-45.

112.   Gazzaruso, C., et al., *Transcutaneous oxygen tension as a potential predictor of cardiovascular events in type 2 diabetes: comparison with ankle-brachial index.* Diabetes Care, 2013. **36**(6): p. 1720-5.

113.   Fosse, S., et al., *Incidence and characteristics of lower limb amputations in people with diabetes.* Diabet Med, 2009. **26**(4): p. 391-6.

114. Fossaceca, R., et al., *Endovascular treatment of diabetic foot in a selected population of patients with below-the-knee disease: is the angiosome model effective?* Cardiovasc Intervent Radiol, 2013. **36**(3): p. 637-44.

115. Forsythe, R.O. and R.J. Hinchliffe, *Management of peripheral arterial disease and the diabetic foot.* J Cardiovasc Surg (Torino), 2014. **55**(2 Suppl 1): p. 195-206.

116. Ferraresi, R., et al., *Long-term outcomes after angioplasty of isolated, below-the-knee arteries in diabetic patients with critical limb ischaemia.* Eur J Vasc Endovasc Surg, 2009. **37**(3): p. 336-42.

117. Faglia, E., et al., *Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003.* Eur J Vasc Endovasc Surg, 2005. **29**(6): p. 620-7.

118. Claesson, K., T. Kolbel, and S. Acosta, *Role of endovascular intervention in patients with diabetic foot ulcer and concomitant peripheral arterial disease.* Int Angiol, 2011. **30**(4): p. 349-58.

119. Ciccone, M.M., et al., *Interventional therapy in diabetic foot: risk factors, clinical events and prognosis at one year follow-up (a study of 103 cases).* Pak J Biol Sci, 2012. **15**(16): p. 789-94.

120. Cardaioli, P., et al., *Endovascular treatment of diabetic foot syndrome: results from a single center prospective registry using mixed coronary and peripheral techniques and equipment.* J Interv Cardiol, 2011. **24**(6): p. 562-8.

121. Caravaggi, C., et al., *Management of ischemic diabetic foot.* J Cardiovasc Surg (Torino), 2013. **54**(6): p. 737-54.

122. Aragon-Sanchez, J., et al., *The role of a specialized approach for patients with diabetes, critical ischaemia and foot ulcers not previously considered for proactive management.* Diabet Med, 2011. **28**(10): p. 1249-52.

123. Alexandrescu, V., et al., *A reliable approach to diabetic neuroischemic foot wounds: below-the-knee angiosome-oriented angioplasty.* J Endovasc Ther, 2011. **18**(3): p. 376-87.

124. Alexandrescu, V. and G. Hubermont, *The challenging topic of diabetic foot revascularization: does the angiosome-guided angioplasty may improve outcome.* J Cardiovasc Surg (Torino), 2012. **53**(1): p. 3-12.

125. Alexandrescu, V. and G. Hubermont, *Primary infragenicular angioplasty for diabetic neuroischemic foot ulcers following the angiosome distribution: a new paradigm for the vascular interventionist?* Diabetes Metab Syndr Obes, 2011. **4**: p. 327-36.

126. Albayati, M.A. and C.P. Shearman, *Peripheral arterial disease and bypass surgery in the diabetic lower limb.* Med Clin North Am, 2013. **97**(5): p. 821-34.

127. Taylor, S.M., et al., *Contemporary management of diabetic neuropathic foot ulceration: a study of 917 consecutively treated limbs.* J Am Coll Surg, 2011. **212**(4): p. 532-45; discussion 546-8.

128. Mannucci, E., et al., *Is glucose control important for prevention of cardiovascular disease in diabetes?* Diabetes Care, 2013. **36 Suppl 2**: p. S259-63.

129.   Tsiara, S., M. Elisaf, and D.P. Mikhailidis, *Influence of smoking on predictors of vascular disease.* Angiology, 2003. **54**(5): p. 507-30.

130.   Apelqvist, J. and C.D. Agardh, *The association between clinical risk factors and outcome of diabetic foot ulcers.* Diabetes Res Clin Pract, 1992. **18**(1): p. 43-53.

131.   Benotmane, A., et al., *Diabetic foot lesions: etiologic and prognostic factors.* Diabetes Metab, 2000. **26**(2): p. 113-7.

132.   Gurlek, A., et al., *Amputation rate in 147 Turkish patients with diabetic foot: the Hacettepe University Hospital experience.* Exp Clin Endocrinol Diabetes, 1998. **106**(5): p. 404-9.

133.   Kerstein, M.D. and E.D. Reis, *Lower-extremity wounds. 2. Management options.* J Wound Care, 2001. **10**(10): p. 401-4.

134.   Korzon-Burakowska, A. and P. Dziemidok, *Diabetic foot - the need for comprehensive multidisciplinary approach.* Ann Agric Environ Med, 2011. **18**(2): p. 314-7.

135.   Ramanujam, C.L., et al., *Split-thickness skin grafts for closure of diabetic foot and ankle wounds: a retrospective review of 83 patients.* Foot Ankle Spec, 2010. **3**(5): p. 231-40.

136.   Wu, S.C., et al., *Foot ulcers in the diabetic patient, prevention and treatment.* Vasc Health Risk Manag, 2007. **3**(1): p. 65-76.

137.   Yesil, S., et al., *Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort.* Hormones (Athens), 2009. **8**(4): p. 286-95.

138.	Friedrich, L. and N. Collins, *Nutrition 411: the diabetic foot ulcer--can diet make a difference?* Ostomy Wound Manage, 2013. **59**(11): p. 10-2.

139.	Posthauer, M.E., B. Dorner, and N. Collins, *Nutrition: a critical component of wound healing.* Adv Skin Wound Care, 2010. **23**(12): p. 560-72; quiz 573-4.

140.	Pscherer, S., et al., *Amputation rate and risk factors in type 2 patients with diabetic foot syndrome under real-life conditions in Germany.* Prim Care Diabetes, 2012. **6**(3): p. 241-6.

141.	Stadelmann, W.K., A.G. Digenis, and G.R. Tobin, *Impediments to wound healing.* Am J Surg, 1998. **176**(2A Suppl): p. 39S-47S.

142.	Wissing, U. and M. Unosson, *The relationship between nutritional status and physical activity, ulcer history and ulcer-related problems in patients with leg and foot ulcers.* Scand J Caring Sci, 1999. **13**(2): p. 123-8.

143.	Adler, A.I., et al., *Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis.* Diabetologia, 2010. **53**(5): p. 840-9.

144.	Apelqvist, J., J. Larsson, and C.D. Agardh, *Medical risk factors in diabetic patients with foot ulcers and severe peripheral vascular disease and their influence on outcome.* J Diabetes Complications, 1992. **6**(3): p. 167-74.

145.	Boulton, A.J., *Lowering the risk of neuropathy, foot ulcers and amputations.* Diabet Med, 1998. **15 Suppl 4**: p. S57-9.

146.	Christman, A.L., et al., *Hemoglobin A1c predicts healing rate in diabetic wounds.* J Invest Dermatol, 2011. **131**(10): p. 2121-7.

147.   Edmonds, M., *Diabetic foot ulcers: practical treatment recommendations.* Drugs, 2006. **66**(7): p. 913-29.

148.   Hess, C.T., *Management of a diabetic foot ulcer.* Adv Skin Wound Care, 2001. **14**(1): p. 18.

149.   Highlander, P. and A.B. Shinabarger, *Perioperative laboratory assessment of diabetic foot infections undergoing amputation: a systematic review.* Foot Ankle Spec, 2013. **6**(6): p. 465-70.

150.   Holt, P., *Assessment and management of patients with diabetic foot ulcers.* Nurs Stand, 2013. **27**(27): p. 49-55; quiz 56, 58.

151.   Imran, S., R. Ali, and G. Mahboob, *Frequency of lower extremity amputation in diabetics with reference to glycemic control and Wagner's grades.* J Coll Physicians Surg Pak, 2006. **16**(2): p. 124-7.

152.   Lacle, A. and L.F. Valero-Juan, *Diabetes-related lower-extremity amputation incidence and risk factors: a prospective seven-year study in Costa Rica.* Rev Panam Salud Publica, 2012. **32**(3): p. 192-8.

153.   Lepore, G., et al., *Poor glucose control in the year before admission as a powerful predictor of amputation in hospitalized patients with diabetic foot ulceration.* Diabetes Care, 2006. **29**(8): p. 1985.

154.   Malik, A., Z. Mohammad, and J. Ahmad, *The diabetic foot infections: biofilms and antimicrobial resistance.* Diabetes Metab Syndr, 2013. **7**(2): p. 101-7.

155.   Markuson, M., et al., *The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes.* Adv Skin Wound Care, 2009. **22**(8): p. 365-72.

156.   Marston, W.A., *Risk factors associated with healing chronic diabetic foot ulcers: the importance of hyperglycemia.* Ostomy Wound Manage, 2006. **52**(3): p. 26-8, 30, 32 passim.

157.   Millington, J.T. and J. Ellenzweig, *The comprehensive therapy of diabetic foot ulcers.* Compr Ther, 2005. **31**(1): p. 50-8.

158.   Philbin, T.M., G.C. Berlet, and T.H. Lee, *Lower-extremity amputations in association with diabetes mellitus.* Foot Ankle Clin, 2006. **11**(4): p. 791-804.

159.   Posthauer, M.E., *Diet, diabetes, and wound management: how important is glycemic control?* Adv Skin Wound Care, 2004. **17**(4 Pt 1): p. 171-2.

160.   Rozsos, I., et al., *The basic and the practical way of treating of diabetic foot.* Acta Chir Hung, 1997. **36**(1-4): p. 299-301.

161.   Watts, S.A., et al., *The effect of age, gender, risk level and glycosylated hemoglobin in predicting foot amputation in HMO patients with diabetes.* J Am Acad Nurse Pract, 2001. **13**(5): p. 230-5.

162.   Winkley, K., et al., *Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer.* J Diabetes Complications, 2007. **21**(6): p. 341-9.

163.   Younes, N.A. and A.T. Ahmad, *Diabetic foot disease.* Endocr Pract, 2006. **12**(5): p. 583-92.

164.   Abdul-Ghani, M., et al., *Increased prevalence of microvascular complications in type 2 diabetes patients with the metabolic syndrome.* Isr Med Assoc J, 2006. **8**(6): p. 378-82.

165. Boyko, E.J., et al., *A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study.* Diabetes Care, 1999. **22**(7): p. 1036-42.

166. Qari, F.A. and D. Akbar, *Diabetic foot: presentation and treatment.* Saudi Med J, 2000. **21**(5): p. 443-6.

167. Yki-Jarvinen, H., et al., *Severity, duration, and mechanisms of insulin resistance during acute infections.* J Clin Endocrinol Metab, 1989. **69**(2): p. 317-23.

168. Jorneskog, G., K. Brismar, and B. Fagrell, *Pronounced skin capillary ischemia in the feet of diabetic patients with bad metabolic control.* Diabetologia, 1998. **41**(4): p. 410-5.

169. Nagareddy, P.R., et al., *Hyperglycemia promotes myelopoiesis and impairs the resolution of atherosclerosis.* Cell Metab, 2013. **17**(5): p. 695-708.

170. Song, J. and K. Chung, *Observational Studies: Cohort and Case-Control Studies.* Plast Reconstr Surg, 2010. **126**(6): p. 2234-2242.

APPENDIX A   **Research Questions and Hypothesis for Each of the Potential Detriments to Healing a DFU**

Glycemic Control - Is poor glycemic control a detriment to the healing of a DFU?

Nutrition - Is poor nutrition/abnormal biomarkers a detriment to the healing of a DFU?

Vascular Supply - Does revascularization of the foot improve healing of DFU where ischemia is present?

Smoking – Does smoking act as a detriment to the healing of a DFU?

Offloading - Does offloading with a total-contact cast improve the healing of a DFU?

Deformity - Does deformity correction (specifically a tendo-achilles lengthening for a tight tendon-achilles) improve DFU healing?

Infection - Is a deep or superficial infection a detriment to the healing of a DFU?

*Note the hypothesis for each research question was that the detriment to healing would have a negative impact or that correcting the detriment would have a positive impact on the outcome.

Dalhousie University - Multidisciplinary Leg Ulcer Care (MDLUC) Initial Assessment Tool

Dalhousie University - Multidisciplinary Leg Ulcer Care (MDLUC) Assessment

Demographics

Do you live alone: ☐Y ☐N

Marital Status:_____

Partners name:_____

Do you have difficulty attending appointments:
☐Y ☐N
If yes, why?_____

Employment status:
☐Full-time
☐Part-time
☐Retired
☐Student
☐Unemployed
☐Disability

Occupation:
_____

Do you work shifts: ☐Y ☐N
Which?_____

Job Activity:
☐Active
☐Somewhat active
☐Sedentary

Family Physician:
_____

Medical History

Duration of present ulcer:_____
☐Improving ☐Worsening
☐No change
Previous ulcers: _____

Current/Previous treatments:
_____
_____
_____
_____
_____

Foot /Nail care by professional?__
Who?_____

Medical Coverage for:
☐Medications ☐PT ☐OT
☐Orthotics
% coverage:

Medical Problems:
☐Coronary Artery Disease
☐Peripheral Vascular Disease
☐Diabetes Mellitus
☐Renal disease ☐dialysis
☐Previous amputation
☐Neuropathy
☐Neuropathic pain
☐Other:
_____
_____
_____

Previous Surgery:
_____
_____

Level of physical activity:
☐Active ☐Somewhat active
☐Inactive

Medications:
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Allergies:
_____
_____

Alcohol use:_____

Recreational drug use: _____

Vascular Assessment

Pulses present by:
☐Palpation or ☐Doppler
       Right: ☐DP ☐PT
       Left: ☐DP ☐PT

Venous insufficiency:
☐Peripheral edema
☐ Loss of ankle ROM

☐Compression stockings

☐ Non-invasive vascular studies

Abn   Date:
       ABI: R _____
              L _____

Check all that apply:
☐ Previous DVT
☐ Cellulitis
☐ Pallor
☐ Cyanosis

☐ Hair loss
☐ Shiny skin
☐ Dependant Rubor
☐ Intermittent Claudication

Abn   ☐ Consult Vascular
              Surgery

☐ Prolonged
Capillary Refill

**Dalhousie University -
Multidisciplinary Leg
Ulcer Care (MDLUC)
Assessment**

Assessment for Infection

Clinical and Radiographic
Findings of Infections:
☐ Fever
☐ Increased pain   If present
☐ Unexplained increase in BG
☐ Erythema
☐ Swelling
☐ Purulent Drainage
☐ Xray fidings of osteomyelitis
☐ Able to probe to bone

☐ Start oral antibiotics:
    ☐ Amoxycillin/Clavulanate 875/125 mg po BID
    ☐ Cephalexin 500 mg po QID & Metronidazole
       500 mg po BID
    ☐ Other:_____
☐ WBC, ESR & CRP
☐ MRI
☐ Bone and Indium scan
☐ Consult Infectious Diseases

MRI – abscess or osteomyelitis, or,
purulent drainage

☐ Consult Orthopedic Surgery

Assessment of External Pressure and need for Offloading

Currently using:
☐ Custom Orthotic
☐ Aircast boot   If none
☐ Offloader   selected
☐ Casting
☐ Brace
☐ Gait aid:_____
☐ Other:_____
_____
_____

☐ Referral to:
_____
Device requested:
_____
_____
_____
_____
_____

Footwear
Type of Shoe:
_____
☐ adequate toe box
☐ pressure from shoe
Where?
_____

Other Source of External
Pressure:
_____
_____

Assessment for deformity

Select all that apply:
☐ Tight Tendo-Achilles   ☐ Hallux valgus
☐ Claw toes   ☐ Hammer toes   If present   ☐ Consult Orthopedic
☐ Rockerbottom foot   ☐ Overlaping digits   Surgery
☐ Pes planus   ☐ Previous ampuations:
                          _____

Glucose Control

HbA1C:
Date: Abn   ☐ Consult
   if unavailable   Endocrinology
☐ HbA1C

☐ Never previously
attended Diabetes
Management Clinic   If present   ☐ Referral to
☐ Unreliable daily skin   DMC
Inspection
☐ Non-compliance with meds

**Dalhousie University -
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Assessment**

Nutrition and Biomarkers			
Has patient ever had an assessment by a dietician? □Y □N If N	Recent bloodwork: □ WBC _____ □ Hg _____ □ ESR/CRP _____ □ HbA1C _____ □Fe _____ □ Alb _____ □ Other:_____	If 2+ abN If incomplete: □ initiate B/W	□ Consult Dietician/Family Physican
If yes, when/why:_____ _____			

Smoking Cessation			
Smoker? □Y □N If Y If yes, how many? _____	□ Counseled Referred to: □ Cessation Program □ Family Physician		□ Reformed Smoker Duration of smoking: _____ Date quit: _____

Other			
Is patient experiencing high levels of stress or anxiety? □Y □N If so, recommendations: _____	□ Local malignancy □ Other malignancy □ Local RTX □ Systemic Chemotherapy	□ Pyoderma □ Vasculities □ Steroid use □ DMARD □ Other : _____	□ Action initiated: _____ _____ _____ _____ _____

Characterize Ulcer		
Mark location of ulcer and R/L Use + to indicate positive location of monofilament testing Autonomic: □ Normal □ Dry/scaly skin □ Maceration between toes □ Loss of hair □ Thickened toenails	Motor: □ Normal (Indicate where abN) □ Ankle (R/L) □ Hindfoot (R/L) □ Midfoot (R/L) □ Forefoot (R/L) DTR: □ Normal (Indicate where abN) □ Patellar (R/L) □ Achilles (R/L) Foot drop: □R □L Loss of protective sensation: □R □L	Strauss Classification: Appearance □ Red (2) □ White/Yellow (1) □ Black (0) Size □ Less than thumb (2) □ Thumb to fist (1) Depth □ Skin (2) □ Tendon (1) □ Bone (0) Infection □ Colonized (2) □ Cellulitis (1) □ Pus/Septic (0) Perfusion □ Pulse (2) □ Doppler (1) □ None (0)

Dalhousie University -
Multidisciplinary Leg
Ulcer Care (MDLUC)
Assessment

Leg Ulcer Measurement Tool (LUMT)

Clinician Rated Domains

Domain	Rating	Domain	Rating
Exudate Type	0 None 1 Serosanguinoues 2 Serous 3 Seropurulent 4 Purulent	Granulation tissue type	0 Healed 1 Bright beefy red 2 Dusky pink 3 Pale 4 Absent
Exudate Amount	0 None 1 Scant 2 Small 3 Moderate 4 Copious	Granulation tissue amount	0 Healed 1 76 to 100% of wound bed 2 51 to 75% of wound bed 3 26 to 50% of wound bed 4 0 to 25% of wound bed
Size (from edge of advancing border of epithelium) (length x width)	0 Healed 1 <2.5 cm2 2 2.5-5.0 cm2 3 5.1-10.0 cm2 4 10.1 cm2 or more	Edges	0 Healed 1 >/= 50% advancing border of epithelium or indistinct borders 2 <50% advancing border of epithelium 3 Attached, no advancing border of epithelium 4 Unattached or undermined
Depth (tissue layers)	0 Healed 1 Partial thickness skin loss 2 Full thickness 3 Tendon/joint capsule visible 4 Probes to bone	Periulder skin: -callus -dermatitis (pale) -maceration -induration -erythema -purple blanchable -purple non-blanchable -skin dehydration	Number of factors affected: 0 None 1 One only 2 Two or three 3 Four or five 4 Six or more
Undermining (greatest at _____ o'clock)	0 0 cm 1 >0-0.4 cm 2 >0.4-0.9 cm 3 >0.9 – 1.4 cm 4 >1.5 cm	Leg edema type	0 None 1 Non-pitting/firm 2 Pitting 3 Fibrosis or lipodermasclerosis 4 Indurated
Necrotic tissue type	0 None 1 Loose white to yellow shough 2 attached white to yellow shough or fibrin 3 soft gret to black eschar 4 hard dry black eschar	Leg edema location	0 None 1 Localized periulcer 2 Foot, including ankle 3 To mid calf 4 To knee
Necrotic tissue amount	0 None visible 1 1 to 25% of wound bed 2 26 to 50% of wound bed 3 51 to 75% of wound bed 4 76-100% of wound bed	Assessment of bioburden	0 Healed 1 Lightly colonized 2 Heavily colonized 3 Localized infection 4 Systemic infection

Dalhousie University - Multidisciplinary Leg Ulcer Care (MDLUC) Assessment

Leg Ulcer Measurement Tool (LUMT)

Patient (Proxy) Rated Domains

Pain amount (as it relates to the leg ulcer) *Rate your pain experience in the last 24 hours on a scale from 0 to 10, where 0 is "no pain" and 10 is the "worst pain*	Numerical rating scale (0-10) 0 None 1 1-2 2 3-4 3 5-7 4 >7		**Total Clinician Rated Domains**
Pain frequency (as it relates to the leg ulcer) *Which of the following best describes how often you have had pain in the last 24 hours?*	0 None 1 Occasional 2 Position dependent 3 Constant 4 Disturbs sleep		**Total Patient Rated Domains**
Quality of life (as it relates to the leg ulcer) *How do you feel about the quality of your life at the present time?*	0 Delighted 1 Satisfied 2 Mixed 3 Dissatisfied 4 Terrible		

Dressing Recommendations

Skin Prep:
- ☐ Barrier wipe
- ☐ Hydrocolloid powder/wafer

- ☐ Transparent film spray
- ☐ Sterile drape

Non-adherent:
- ☐ Non-Adherent Synthetic
- _____
- ☐ Silicone
- _____
- ☐ Mesh
- _____

Antimicrobial
- ☐ Chlorhexidine
- ☐ Cadexomer Iodine
- ☐ Silver _____
- ☐ Other _____

Exudate –

Dry:
- ☐ Transparent film _____
- ☐ Hydrogel _____
- ☐ Hydrocolloid _____

Moderate:
- ☐ Composite dressing _____
- ☐ Hypertonic dressing_____
- ☐ Foam _____

High:
- ☐ Alginate _____
- ☐ Hypertonic dressing _____
- ☐ Hydrophilic fiber _____

Odour control:
- ☐ Charcoal _____

Other:_____
_____

Frequency:

Negative Pressure Wound Therapy

Skin Prep:
- ☐ Barrier wipe
- ☐ Hydrocolloid powder/wafer
- ☐ Transparent film spray
- ☐ Sterile drape

Dressing type:
- ☐ Black foam
- ☐ White foam
- ☐ Silver foam
- ☐ Packing to sinus
- ☐ Mesh _____
- ☐ Chlorhexidine gauze

Pressure: _____
Intensity: _____
- ☐ Continuous
- ☐ Intermittent

☐PICO   ☐ VAC   ☐Other: _____

**Dalhousie University -
Multidisciplinary Leg
Ulcer Care (MDLUC)
Assessment**

Summary of Initial Visit

Baseline Investigations:
(check indicates completed)
☐ Weight-bearing Foot X-ray
☐ Hg
☐ WBC
☐ ESR, CRP
☐ HbA1C
☐ Serum Albumin
☐ Other:
_____
_____

Advanced Imaging ordered:
☐ Bone/Indium scan
☐ MRI
☐ Non-invasive vascular studies

Consultations initiated:
☐ Orthopedics
☐ Vascular surgery
☐ Infectious diseases
☐ Endocrine

    If none selected

☐ Consult Plastic Surgery (Coverage/
Soft tissue procedure)

Allied Health initiated:
☐ Orthotist
☐ Diabetes Education
☐ Smoking Cessation Program
☐ Social Services
☐ Other:
_____
_____
_____

Summary of Potential Detriments to
healing:

Vascular supply:
☐ Optimized   ☐ Not yet optimized

Infection:
☐ Optimized   ☐ Not yet optimized

External Pressure and Offloading:
☐ Optimized   ☐ Not yet optimized

Deformity:
☐ Optimized   ☐ Not yet optimized

Glucose Control:
☐ Optimized   ☐ Not yet optimized

Nutrition and Biomarkers:
☐ Optimized   ☐ Not yet optimized

Smoking:
☐ Optimized   ☐ Not yet optimized

Other:
☐ Optimized   ☐ Not yet optimized

Dalhousie University - Multidisciplinary Leg Ulcer Care (MDLUC) Assessment

Vascular Assessment		
☐ Non-invasive Vascular Studies Results:	☐ Consultation with Vascular Surgery Date: Recommendations:	☐ Vascular Supply Optimized

Assessment for Infection		
☐ Antibiotics Which/Duration: _____ – _____ – _____ –	☐ Consultation with Orthopedic Surgery Date: Recommendations:	☐ Infection Optimized
Bloodwork Results: ☐ WBC: _____ ☐ ESR: _____ ☐ CRP: _____ ☐ Imaging Results:	☐ Consultation with Infectious Diseases Date: Recommendations:	

External Pressure and Offloading		
Currently using: ☐ Custom Orthotic _____ ☐ Aircast boot ☐ Offloader _____ ☐ Casting ☐ Brace ☐ Gait aid: _____ ☐ Other: _____ _____ ☐ Shoe wear modification _____ ☐ Other: _____	Comments:	☐ External Pressure and Offloading Optimized

**Dalhousie University -
Multidisciplinary Leg
Ulcer Care (MDLUC)
Assessment**

Deformity	☐ Notes:	☐ Deformity Optimized
☐ Consultation with Orthopedic Surgery Date: Recommendations:		
Glucose Control	☐ Consult Endocrinology Recommendations:	☐ Glucose Control Optimized
☐ HbA1C:		
Nutrition and Biomarkers	☐ Nutritional assessment Notes:	☐ Nutrition/Biomarkers Optimized
☐ Recent bloodwork:		
Smoking Cessation	Comments:	☐ Smoking Optimized
☐ Consultation with FP or Cessation program		
Other		☐ All "other" optimized
Comments:		

Notes

Dalhousie University -
Multidisciplinary Leg
Ulcer Care (MDLUC)
Assessment

Characterize Ulcer

Mark location of ulcer and R/L
Use + to indicate positive location of
monofilament testing

Autonomic: ☐ Normal
☐ Dry/scaly skin
☐ Maceration between toes
☐ Loss of hair
☐ Thickened toenails

Motor: ☐ Normal
(Indicate where abN)
☐ Ankle (R/L)
☐ Hindfoot (R/L)
☐ Midfoot (R/L)
☐ Forefoot (R/L)

DTR: ☐ Normal
(Indicate where abN)
☐ Patellar (R/L)
☐ Achilles (R/L)

Foot drop:
☐ R   ☐ L

Loss of protective
sensation:
☐ R   ☐ L

Strauss Classification:

Appearance
☐ Red (2)
☐ White/Yellow (1)
☐ Black (0)
Size
☐ Less than thumb (2)
☐ Thumb to fist (1)
Depth
☐ Skin (2)
☐ Tendon (1)
☐ Bone (0)
Infection
☐ Colonized (2)
☐ Cellulitis (1)
☐ Pus/Septic (0)
Perfusion
☐ Pulse (2)
☐ Doppler (1)
☐ None (0)

Dressing Recommendations

Skin Prep:
☐ Barrier wipe
☐ Hydrocolloid powder/
wafer

☐ Transparent film spray
☐ Sterile drape

Non-adherent:
☐ Non-Adherent Synthetic
_____
☐ Silicone
_____
☐ Mesh
_____

Antimicrobial
☐ Chlorhexidine
☐ Cadexomer Iodine
☐ Silver _____
☐ Other _____

Exudate –
Dry:
☐ Transparent film _____
☐ Hydrogel _____
☐ Hydrocolloid _____

Moderate:
☐ Composite dressing _____
☐ Hypertonic dressing_____
☐ Foam _____

High:
☐ Alginate _____
☐ Hypertonic dressing _____
☐ Hydrophilic fiber _____

Odour control:
☐ Charcoal _____

Other:_____
_____

Frequency:

Negative Pressure Wound Therapy

Skin Prep:
☐ Barrier wipe
☐ Hydrocolloid powder/wafer
☐ Transparent film spray
☐ Sterile drape

Dressing type:
☐ Black foam
☐ White foam
☐ Silver foam
☐ Packing to sinus
☐ Mesh _____
☐ Chlorhexidine gauze

Pressure: _____
Intensity: _____
☐ Continuous
☐ Intermittent

☐PICO   ☐ VAC   ☐Other:

APPENDIX D   Data Dictionary

		Source	Type	Details
Demographics	Patient ID (non-identifiable, unique)	Assigned at time of enrollment	Categorical	
	Visit (Interval data)		Categorical	Initial 2 months 4 months 6 months
	Age (ratio, in years)		Categorical	
	Gender		Categorical	Male (M) or Female (F)
Exposure	HbA1c (%)	HPF, interval data	Categorical	Range 5.0 – 19.0
Primary Outcome	Ulcer Healing (Ratio Values, recorded in days)	Follow up visit		
Secondary Outcome	Leg Ulcer Measurement Tool (LUMT) - Validated tool to evaluate a leg ulcer appearance	Clinician Rated Domains - ordinal values, obtained from LUMT located in patient pathways - Data available from clinical pathway as scored by clinical nurse specialist (CNS)		14 items, scored by physicians (exudate type, amount, size, depth, undermining, necrotic tissue, granulation type and amount, edges, peri-ulcer skin, leg edema type, location, bioburden) - each item is scored from 0-4 - sum totals recorded, range of values 0-56
		Patient Rated Domains - ordinal values, obtained from LUMT located in patient pathways - data available from clinical pathway, score reported by patient		3 domain areas scored from 0-4 (pain amount, pain frequency, quality of life) - range of values 0-12
	SF-36 - global health			Physical Component Score –

	survey measurement tool of 36 items that compose 8 scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) that are combined to produce two component scores			ratio values 0-100, transformed into norm based score (Mean = 50, SD = 10) Mental Component Score – ratio values 0-100 transformed into norm based score (Mean = 50, SD = 10)
	Cardiff Wound Impact Schedule (CWIS) - disease specific quality of life measurement tool for patients with diabetic foot ulcers			Four domains of measurement (quality of life, well-being, daily living, physical symptoms) - items summed and averaged for each domain, range 0-100

Confounders:

		Source	Type	Details
Vascular Supply	Palpable Pulse	Obtained from clinical exam		Dichotomous ordinal data, reported as Y or N
	Arterial Brachial Index - non-invasive test of vascular supply, ratio of blood pressure in lower leg to arm			Value range = <0.5 (minimum) to >1.2 (maximum) - values between maximum and minimum values reported to single decimal point
	Revascularizati on			Dichotomous ordinal data,

	- indicates whether or not a surgical intervention has taken place to re-establish vascular supply to limb with DFR present			reported as Y or N
Infection	Clinical Findings - clinical findings consistent with infection (erythema, fever, purulent drainage	Available from clinical pathway as reported by CNS		Nominal data, reported as Y or N
	Antibiotics - patient is currently on or has had antibiotic therapy initiated at the current visit	Available from clinical pathway as reported by CNS		Nominal data, reported as Y or N
	White Blood Cell Count (WBC, unit=cells/mm) - indicates the number of leukocytes present in the blood - surrogate marker for infection when elevated			Interval scale - value range 0-35, with value of >10 considered elevated
	Erythrocyte Sedimentation Rate (ESR, unit = mm/hr) - the rate at which erythrocytes sediment over a one hour period of time - surrogate	Obtained from HPF		Interval scale - value range 0-100, value >20 considered elevated

	marked for infection			
	C-Reactive Protein (CRP, unit mg/L) - pentameric protein found in plasma in pro-inflammatory states - surrogate marker for infection when elevated	Obtained from HPF		Interval scale - value range 0-200, value >2 considered elevated
Offloading	Offloading - lifestyle modification or physical aid to reduce the external pressure at the active ulcer site	Obtained from clinical pathway as indicated by CNS		Nominal scale, reported as Y, N or N/A
	Type - indicate type of offloading device employed	Obtained from clinical pathway as indicated by CNS		Nominal scale, devices include: - custom orthotic - aircast boot - offloader - cast - bracing - gait aid - shoewear modifications - other
Deformity	Clinical assessment of amount of change in foot shape from baseline			Nominal scale, descriptors include: - tight tendo-achilles - claw toes - rocker-bottom foot - pes planus - hallux valgus - hammer toes - overlapping digits

				- previous amputations - other - none
Nutrition/Bio markers (WBC, ESR, Fe, Albumin, Hgb)	WBC, ESR, CRP (as indicated in infection section)			
	Serum Iron (Fe, unit = ug/dL) - measure of body iron stores - abnormality indicates poor prognosis with regards to biomarkers			Reference range 1 – 200, value less than 170 considered abnormal
	Albumin (unit = U/L) - globular protein produced by liver - surrogate marker of nutrition			Value <3.5 considered abnormal
	Hemoglobin (Hgb, unit = g/L) - oxygen-transport protein on RBC - biomarker,			Range 1-200, values less than 120 considered abnormal
Smoking		Obtained from clinical pathways as reported by CNS		Smoking status indicated as Y or N - nominal scale
Ulcer Characteristics (Coronal plane, anatomic, measurement, Strauss)	Coronal Plane - location of ulcer indicated as either dorsal or plantar surface	Obtained from clinical pathways as reported by CNS		Nominal data
	Anatomic Location - location of	Obtained from clinical pathways as reported by CNS		Nominal data - hindfoot (proximal to Chopart joint)

	ulcer			- midfoot (between Chopart joint and metatarsals) - forefoot (distal to metatarsals)
	Measurement (unit = cm) - cross-sectional measurements (diameter) in two planes (length and width)			Ratio scale

	Strauss Classification
	- graded classification for open ulcers
				Interval scale
				- assigned score 0-2 for each of the following domains:
				  - appearance
				  - size
				  - depth
				  - infection
				  - perfusion
				- value range 0-10

APPENDIX E   **Simulation Code in R Statistical Software and Results from Simulation for Sample Size Calculation**

Simulation Code in R Statistical Software:
```
n<-130
asim<-10000
pval<-rep(NA,asim)
corval<-rep(NA,asim)
hazval<-rep(NA,asim)
for(i in 1:asim)
{
gm<-rgamma(n,shape=.63,scale=200)
gmstd<- (gm-mean(gm))/var(gm)^.5
z<-rnorm(n,8.1,1.3)
x<-z+.4 * gmstd
cns<-(gm<180)
cph<-coxph(Surv(gm,cns)~x)
summary(cph)
pval[i]<-summary(cph)$coefficients[5]
corval[i]<-cor(gm,x)
hazval[i]<-summary(cph)$conf.int[2]
}

summary(cph)
summary(pval)
quantile(pval,.8)
summary(corval)
hist(corval)
summary(hazval)
hist(hazval)
```

Results from simulation:
Power 0.04181843
```
> summary(pval)
 Min. 1st Qu. Median Mean 3rd Qu. Max.
0.0000000 0.0005174 0.0045210 0.0396200 0.0267800 0.9920000
> quantile(pval,.8)
 80%
0.04181843
```

Effect size 0.2941
```
> summary(corval)
```

Min. 1st Qu. Median Mean 3rd Qu. Max.
-0.01412 0.24160 0.29610 0.29410 0.34820 0.59250

Hazard Ratio 1.2420
> summary(hazval)
Min. 1st Qu. Median Mean 3rd Qu. Max.
0.9437 1.1780 1.2370 1.2420 1.2990 1.6890

APPENDIX F   Logistic Regression Analysis

Categorical Variables Codings

		Frequency	Parameter coding (1)	Parameter coding (2)
VascOptimized	.00	63	.000	.000
	1.00	7	1.000	.000
	2.00	20	.000	1.000
OPTIMIZED	.00	78	.000	
	1.00	12	1.000	
nSEX	Male	66	.000	
	Female	24	1.000	

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	118.656[a]	.058	.078

a. Estimation terminated at iteration number 3 because parameter estimates changed by less than .001.

APPENDIX G   Cox Regression Analysis

Analysis results for HbA1C categorized as "high" or "low":

Categorical Variable Codings[b],c,d,e,f

		Frequency	(1)	(2)
nSEX[a]	.00=Male	76	0	
	1.00=Female	32	1	
CAT2_HBA1C[a]	.00=0-7.999	54	0	
	1.00=8.0-Highest	54	1	
OPTIMIZED[a]	.00	91	0	
	1.00	17	1	
OffOptimized[a]	.00	40	0	0
	1.00	62	1	0
	2.00	6	0	1
VascOptimized[a]	.00	78	0	0
	1.00	7	1	0
	2.00	23	0	1

a. Indicator Parameter Coding
b. Category variable: nSEX
c. Category variable: CAT2_HBA1C
d. Category variable: OPTIMIZED
e. Category variable: OffOptimized
f. Category variable: VascOptimized

Omnibus Tests of Model Coefficients[a]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
487.233	5.151	8	0.741	3.708	5	0.592	3.708	5	0.592

a. Beginning Block Number 3. Method = Enter

Analysis for HbA1C categorized as "high," "intermediate," or "low"

Categorical Variable Codings[b],c,d,e,f

		Frequency	(1)	(2)
nSEX[a]	.00=Male	80	0	
	1.00=Female	32	1	
CAT3_HBA1C[a]	.00=0-6.5	25	0	0
	1.00=6.501-11	75	1	0
	2.00=11.01-Highest	12	0	1
OPTIMIZED[a]	.00	94	0	
	1.00	18	1	
OffOptimized[a]	.00	40	0	0
	1.00	64	1	0
	2.00	8	0	1
VascOptimized[a]	.00	81	0	0
	1.00	7	1	0
	2.00	24	0	1

a. Indicator Parameter Coding
b. Category variable: nSEX
c. Category variable: CAT3_HBA1C
d. Category variable: OPTIMIZED
e. Category variable: OffOptimized
f. Category variable: VascOptimized

Omnibus Tests of Model Coefficients[a]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
501.162	5.069	9	0.828	3.397	5	0.639	3.397	5	0.639

a. Beginning Block Number 3. Method = Enter