Monitoring and Managing the Offloading, Physical Activity Engagement and Fall Risk of Persons with Diabetic Foot Disease

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Abbreviations

DFU	diabetic foot ulcer
DPN	diabetic peripheral neuropathy
kPA	kilopascal
m	meter
mm	millimetre
PA	physical activity
V	volt

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Contents

Abstract

This thesis integrates a series of previously published papers centring around three interrelated themes addressing the complex relationship between diabetic foot ulcers (DFU) and physical activity engagement. ***The three foci of the thesis include: 1)*** *'offloading' DFU via specialized footwear that limit the application of physical stress to ulcers during weight bearing activity in order to promote healing;* ***2)*** *monitoring and managing physical activity engagement of both patients at risk for DFU and patients with active DFU;* ***3)*** *the heightened risk of falls in individuals at risk for DFU.* A cohesive underlying foundation of the body of work contained within this thesis is an effort to help care providers and patients achieve better physical activity profiles.

Offloading diabetic feet refers to the redistribution of physical stress away from sites at risk for or with active DFU. Thus, it is important to both prevent DFU but also to heal active DFU. This thesis includes two publications pertaining to the objective measurement of patient adherence to offloading modalities as well as two publications regarding the biomechanical assessment of devices used to offload DFU. The need for offloading is necessitated by the fact that individuals with DFU engage in weight bearing physical activity that can inflict physical trauma beyond the tolerance of the soft tissue of their feet, however, the relationship between physical activity and the formation as well as healing of DFU is not fully understood. A series of five publications concerning physical activity within patients with, or at risk for DFU are included in this thesis: two focus on improved monitoring of physical activity and three focus on safely increasing physical activity engagement. Due to a number of interconnected factors, individuals at risk for DFU are also at high risk for falling. The final three publications included in this thesis are devoted to falls risk.

Chapter 1: Introduction

An alarming 9.3% of the global population, equivalent to 463 million people, was estimated to have diabetes in 2019 and that percentage is expected to continue climbing for the foreseeable future[1]. Unfortunately there are numerous serious complications for which patients with diabetes are at risk. One of the most insidious complications is diabetic foot ulcers (DFU), despite the fact that these wounds are a relatively neglected complication[2]. Recent estimates suggest that 19-34% of individuals with diabetes will develop a DFU within their lifetime[3]. The five year survival rate for persons with a diabetic foot ulcer is ~50-60%[2] which is worse than many common types of cancer such as breast and prostate[4]. In addition to having a reduced life expectancy, patients that develop a DFU are at significant risk for a subsequent lower extremity amputation[5-9]. Patients with diabetic foot disease have actually reported fearing a major lower extremity amputation more than death[10]. DFU are exceptionally difficult to heal which helps explain why they precede 84% of amputations in patients with diabetes[11]. Another marker of the burden of DFU is the tremendous fiscal cost of treating them. In the United States, approximately one-third of $237 billion in direct costs for diabetes care in 2017 were associated with foot disease care[12]. In England 0.8-0.9% (£837-962 million) of the National Health Service budget is tied to care for ulcerations and amputations in people with diabetes and >90% of those costs are related to DFU[13].

There are a number of diabetic complications that predispose individuals towards developing DFU[14-17], however, the loss of ‘protective sensation’ due to diabetic peripheral neuropathy (DPN) is commonly the primary factor. DPN induced loss of sensation allows affected individuals to wear a hole in the surface of their feet without feeling any pain, similarly to wearing a hole in a pair of socks[18,19]. Although

DFU sometimes form in response to acute trauma such as extreme temperature exposure or puncture of the plantar tissue by a foreign body, they typically form in response to the cyclical application of physical stress to the feet during weight-bearing physical activity (PA)[18]. Within this perspective, plantar tissue stress has been defined as “the accumulation of all mechanical stresses on an area of plantar foot tissue from all weight-bearing activity over time” (p. 869)[20]. Key factors in quantifying this stress include the vertical loading (pressure), horizontal loading (shear) and the volume of stress (PA). Mueller and Maluf laid out a ‘physical stress theory’ that presents how tissue will respond to a continuum of varying amounts of stress[21]. Negative outcomes are associated with both the low and high ends of the continuum. On the high end, the absence of pain in neuropathic feet allows diabetic individuals to cross the threshold into the excessive stress region of the continuum without their knowledge. This placement of excessive stress on the feet in turn leads to a breakdown of plantar tissue and formation of a diabetic foot ulcer.

1.1: Offloading Diabetic Foot Ulcers

Devices that offload active ulcers redistribute stress away from DFU locations to other plantar regions of the foot and in some cases to the leg as well. The best evidence to date from randomized controlled trials, indicates irremovable knee high devices (either total contact casts or prefabricated cast walkers) yield the best healing outcomes[22-24]. Despite irremovable offloading options being considered the ‘gold standard’ for DFU, multiple studies have found they are used minimally by practitioners[25-27]. One of the reasons reported for not using irremovable knee-high devices is patients’ lack of tolerance for the devices[25,26]. Some of the factors influencing patient tolerance include interference with sleep, self-care, choice of clothing, and mobility/balance. Intervention related barriers to providers’ use of irremovable knee-high devices include secondary complications such as new ulcers and falls, as well as the cost, time, and skill required to dispense the devices[25,26]. A final barrier to the use of irremovable knee-high devices are wound related barriers, such as limited access to wounds for monitoring healing and conducting dressing changes[25,26]. In common practice offloading devices such as removable cast walkers, specialty shoes and felted foam are used more commonly to offload DFU[25-27]. Chapter 2 of this thesis presents four publications[28-31] centred upon the use of removable offloading devices to treat DFU.

1.2: Monitoring and Managing Physical Activity

Although the formation of ulcers on neuropathic feet have long been attributed to the physical stress imparted during weight bearing activity[32], attempts to quantify the stress patients place on their feet in the real world has been a more recent advent. Initial forays into objectively studying the association between PA and DFU utilized pedometers to record the number of steps patients took per day[33,34]. While these initial studies measuring step counts represented a substantial advance over self-reports of PA, these studies still presented a limited assessment of the cycles and duration of stress individuals exposed their feet to over the course of a day. Chapter 3 of this thesis includes two publications[35,36] regarding the advancement of methodologies used to quantify PA engagement in association with DFU. The chapter also includes three additional publications[37-39] regarding efforts to help patients with diabetic foot disease to engage in safe levels of PA from which they can derive the benefits of PA without excessively stressing their feet.

1.3: Falls in Individuals at Risk for Diabetic Foot Ulcers

Like DFU, accidental falls present a tremendous global burden. The World Health Organization (WHO) estimated 283,000 people died due to falls in 2000[40].

The WHO also noted that in all regions of the world adults >70yrs have a significantly higher fall-related mortality rate than younger persons. As the global population aged, the estimated number of deaths due to falls increased to 646,000 in 2018 and by that date the annual number of falls requiring medical attention was ~37.3 million[41]. Chapter 4 of this thesis is centred on the unfortunate association between diabetic foot disease and falls in older adults. The first publication of the chapter discusses how factors such as decreased sensorimotor function, musculoskeletal deficiencies, pain, and therapeutic footwear can increase the risk for falling by older adults with diabetes[42]. The next publication is associated with a study that evaluated an intervention intended to treat the fall-risk factor of DPN[43]. The final publication of the chapter presents a study that assessed the association between DPN and fear of falling[44].

Chapter 2: Diabetic Foot Ulcer Offloading Publications

2.1: Critical Account of Offloading Publications

Although offloading areas of the foot that are prone to high physical stress via specialized footwear and devices is critical to both the prevention of new DFUs and the healing of active DFUs[22,45], the offloading publications in this thesis focus upon offloading active wounds. The first two offloading publications addressed a prior gap in the understanding of why removable offloading devices have poorer healing outcomes. Despite removable cast walkers (RCW) having been shown to offload DFU as well as total contact casts[46,47], RCW have consistently provided poorer healing outcomes[47,48]. Based on the results of these past studies it was assumed that individuals that were provided RCW were choosing not to wear their devices during all weight bearing activity. Although some information regarding patient adherence could be gathered via patients self-reporting, there is a high likelihood that some patients will inflate their reported adherence levels[49]. Therefore, a means to objectively monitor adherence was validated within Publication 1 of this thesis[28].

Publication 1's methodology utilized a waist worn accelerometer to monitor PA engagement. A secondary accelerometer that was time synchronized to the first accelerometer, was affixed to the offloading device (RCW). This secondary accelerometer was concealed upon the RCW and participants were not made aware of its presence. Adherence was determined by whether the RCW's accelerometer registered movement at the times when the waist mounted device registered PA. Although a large number of adherence data samples were collected in Publication 1 (1,851 samples) the data was limited in that it was collected from a single subject and relied on a single accelerometer model. Future studies aimed at replicating the findings of Publication 1 would benefit from the use of multiple subjects and the incorporation of multiple models of accelerometers to confirm whether the results remain consistent across varied subjects and accelerometers.

Publication 1 served as a precursor to Publication 2 and its adherence monitoring methodology was utilized in the study associated with Publication 2 of this thesis[29]. Publication 2 presented the first study to look at the association between DFU healing and offloading adherence in which adherence was treated as a continuous variable. Previous research had dichotomized adherence as either absolute (use of irremovable device) or partial (use of removable device). In contrast, Publication 2's study objectively demonstrated when offloading adherence is considered as a continuous variable it is positively associated with DFU healing. The best predictor of non-adherence the study identified was patients' (N=79) level of self-reported postural instability, hence linking offloading adherence with the risk for falls. In considering the work of Publication 2 (and Publication 1) in today's environment, it is worth noting significant advances have been made in activity monitoring. Were this work to be repeated, newer monitors that capture a much more granular detail of physical activity engagement could be used to provide greater insight into what DFU patients are doing both with and without use of their offloading devices. For example, the activity monitors utilized in chapter 3 of this thesis provided continuous monitoring of body posture allowing for assessment of how much time the feet are loaded while standing and even during periods of sitting.

The next two offloading publications of this thesis dealt with efforts to improve the patient experience with RCW which in turn may lead to improved DFU healing. These studies were undertaken in recognition of the following facts: 1) RCW are used more often than irremovable devices; 2) knee high RCW provide the same functional offloading benefit to DFU as irremovable knee high devices; 3) RCW's poorer DFU healing outcomes are associated with patients choosing not to adherently use them. The first of these studies investigated whether height of RCWs impacted offloading capacity[30]. Individuals at risk for DFU (presence of DPN) have been shown to be physically deconditioned[50]. As RCW are quite heavy relative to normal footwear, one would expect DFU patients to have difficulty walking while wearing RCW. Publication 3 of this thesis found knee high and ankle high RCW provided similar offloading benefit to the forefoot that was superior to a shoe height RCW[30]. The study also provided some preliminary data suggesting balance may have been better in the ankle high RCW than in the knee high RCW. The second of these studies investigating the potential to improve the patient experience with offloading modalities considered two design factors for RCW[31]. As in the first study, it compared ankle high and knee high walkers. In addition to looking at height/size as a factor, Publication 4 of this thesis also considered the imposed limb length discrepancy that the thick rocker bottom soles of RCW induce. The study investigated the use of an external shoe lift for the limb contralateral to the limb using the RCW. The study found the best gait and self-reported comfort outcomes were associated with the ankle high RCW paired with a contralateral shoe lift. Future studies are needed to confirm whether provision of an ankle high RCW paired with a contralateral shoe lift leads to greater offloading adherence and DFU healing than provision of a knee high RCW.

2.2: Publication 1

A Method for Assessing Off-loading Compliance (2009)

2.2.1: Publication 1 Aim

The aim of the study associated with this publication was to validate a method for objectively monitoring patient adherence to offloading devices.

2.2.2: Publication 1 Summary

A single adult subject's adherence to the use of a RCW was assessed during waking hours over four consecutive days (approximately 15.5 hours/day). The subject did not have a DFU and was instructed to alternate use of the RCW and standard footwear several times a day. Each time the RCW was donned or doffed, the subject recorded the time of the event in a diary. The objective adherence monitoring methodology relied on the use of two accelerometry-based activity monitors. One monitor was worn on the subject's clothing at hip level per the device's (Lifecorder Plus; Suzuken Co Ltd, Nagoya, Japan) standard use directions. Each of the activity monitors logged intensity of PA engagement in two minute epochs and the two devices were time synchronized. PA recorded by the hip worn monitor was coded as adherent/non-adherent based upon whether the RCW monitor registered movement at the same time the hip monitor registered movement. The monitoring period consisted of 1,851 two minute epochs and PA was registered during 591 of the epochs. Three different adherence processing schemes were evaluated. The first relied on a simple on/off principal- if the RCW registered any activity at the same time activity was registered by the hip monitor, the subject was considered to have been wearing the RCW during the activity. The other two methods had set ratio cut-offs for assigning adherence. Method two assigned PA as RCW adherent if the RCW monitor's PA for a two minute epoch was greater than half of the value recorded at the hip. The third method assigned PA as RCW adherent if the RCW monitor's PA for a two minute epoch was greater than the value recorded at the hip. PA intensity values were given positive values if the activity had been coded as RCW adherent and the values were negative values if the activity had been coded as non-adherent. A repeated-measures ANOVA was conducted with the four compliance coded PA data sets (1 diary coded and 3 variants coded via RCW monitor) and followed by intraclass correlation calculations of diary coded PA with the three RCW monitor methods. The second methodology of processing the RCW monitor data proved the most accurate, as that data set did not significantly differ from the diary coded data and had a high intraclass reliability value of 0.93.

2.2.3: Publication 1 New Knowledge Gained

The study found the dual activity monitor methodology for objectively monitoring offloading adherence was valid. Having an objective means of measuring adherence is advantageous over self-reporting for two reasons. Self-reporting can be biased by patient recall error. Recall error could be substantial as DFU typically take at least several weeks to heal and often require a period of months to heal. Another potential source of bias with self-reported adherence is intentional errors in reporting. A patients' desire to please their care providers may result in the patient inflating their reported RCW adherence. The adherence monitoring methodology validated in this publication can be of benefit both to future research as well as for patient management.

2.3: Publication 2

The Role and Determinants of Adherence to Offloading in Diabetic Foot Ulcer Healing: a Prospective Investigation (2016)

2.3.1: Publication 2 Aim

The primary aim of the study associated with this publication was to determine whether objectively monitored offloading adherence was associated with DFU healing. The secondary aim was to identify determinants of offloading adherence.

2.3.2: Publication 2 Summary

The study was a prospective multicentre investigation of DFU patients in the UK (n= 46) and US (n = 33). All patients were provided a removable offloading device and told to wear the device during all weight bearing activity. Most patients (77%) received removable cast walkers. Adherence was monitored via the methodology validated in Publication 1 of this thesis[28]. However, the activity monitor placed on offloading modality was concealed from easy identification. In order to limit the likelihood of the Hawthorne effect (altering behaviour in response to being aware one is being observed) impacting adherence results, participants were not notified that offloading adherence was being monitored. Offloading adherence and wound healing were monitored for a period of 6 weeks. If wound healing occurred prior to 6 weeks, adherence monitoring was halted at the study visit at which the wound was determined to have fully healed. Wound healing was assessed by making digital planimetry measurements of digital wound photographs. Patient demographics were collected at baseline and participants also completed three psychological assessments: Neuropathy and Foot Ulcer Quality of Life (NeuroQol) scale[51], Revised Illness Perception Questionnaire (IPQ-R)[52], depressive symptoms 7-item subscale of Hospital Anxiety and Depression Scale (HADS)[53]. Participants' wounds significantly decreased in size over the course of the study (230±288 mm^2 vs. 106±155 mm^2, $p<0.001$) and 19 participants (24%) achieved complete wound closure. The mean monitoring period was 35±10 days.

2.3.3: Publication 2 New Knowledge Gained

The primary aim of Publication 2 was achieved with offloading adherence being found to significantly predict end of study wound size. Other predictors of final wound size were baseline wound size and country of residence (UK participants achieved greater healing). Although baseline wound size being predictive of end of study wound size was not surprising, the difference between UK and US participants was not anticipated. An explanation was not initially noted in Publication 2, however, upon further refection the greater use of healing sandals in the US was identified as likely contributing to this difference. Most of the participants in the study used knee-high removable cast walkers, however, 13 participants used the less efficacious option of healing sandals[24]. The use of sandals was much more prevalent (n=10 vs. n=3) in the US. Publication 2 was also able to achieve its secondary aim of identifying determinants of offloading adherence. Lesser self-reported postural instability, larger and more severe (University of Texas classification[54]) baseline ulcers, higher foot pain and more severe neuropathy were all predictive of greater adherence.

There is one notable difference between the findings of Publication 2 and prior research regarding RCW adherence. In 2003, Armstrong et al. published the results of a single site (Tucson, Arizona USA) study that assessed RCW adherence independently of wound healing[34]. They found their cohort of patients only wore their RCW during 28% of their daily PA. However, in Publication 2 participants adherently used their offloading devices during 59±22% of their PA. The difference between the two studies may in part be due to regional and demographic differences in adherence (which is plausible considering the results of Publication 2) as well as a general improvement in patients' offloading adherence over the intervening time between the two studies.

2.4: Publication 3

Impact of Strut Height on Offloading Capacity of Removable Cast Walkers (2012)

2.4.1: Publication 3 Aim

The primary aim of the study associated with this publication was to determine whether altering the height of a removable cast walker altered the offloading capacity of the device. Gait kinematics while walking in the devices were assessed as secondary exploratory variables.

2.4.2: Publication 3 Summary

Eleven participants with DPN were recruited. Participants had to be able to walk without the use of an assistive device such as a cane and could not have an active DFU at the time of their participation. Each participant completed walking trials in three removable cast walker options and a control condition of bilateral athletic shoes. The removable cast walkers included a knee-high option (DH offloading Walker, Össur Americas, Foothill Ranch, CA), an ankle-high option (Equalizer Walker, Össur Americas, Foothill Ranch, CA) and a shoe option. The ankle-high and shoe options only differed from the knee-high walker in regards to the height of the devices' rigid struts running up the sides of the leg and the height of the soft goods that extended up the leg. The same offloading insole was utilized with each cast walker and each walker utilized the same rocker bottom outsole.

Outcome measures were collected while conducting a 20m walking trial in each footwear condition. The order of footwear was randomized for each participant. In-shoe pressure insoles (Pedar-X; Novel, Munich, Germany) collected foot loading data at 100Hz. Masking software was utilized to identify peak pressure and pressure time integral values for 4 forefoot regions that commonly ulcerate. Repeated measures ANOVAs with main effects of footwear and foot region were used to analyse the peak pressure and pressure time integral data. Gait kinematics variables were collected at 200Hz via an inertial measurement unit system (Physilog, BioAGM, CH). One-way repeated measures ANOVAs were used to compare kinematic parameters while walking in the varied footwear.

There was a significant interaction between footwear and foot region for peak pressure and pressure time integral. Therefore, the effect of footwear within each region as assessed via least significant difference post hoc analyses. Each of the removable cast walker options yielded statistically significant lower peak pressure and pressure time integral values at each of the four foot regions. The ankle-high and knee-high removable cast walkers generally yielded significantly lower pressure values than the shoe cast walker. Although there were some significant pressure differences between the ankle-high and knee-high cast walkers, overall their offloading performance was quite similar. The only statistically significant kinematic outcome was a 12% decrease in velocity while walking in the knee-high removable cast walker relative to the standard shoes (p=0.028). Although differences were not significant, there was a trend of the ankle-high cast walker yielding a smaller range of centre of mass rotation (18% medial/lateral and 22% anterior/posterior) than the knee-high cast walker.

2.4.3: Publication 3 New Knowledge Gained

The offloading capacities of the ankle-high and knee-high removable cast walkers were similar to that observed in prior cast walker research[46], however, the finding that the ankle-high and knee-high cast walkers were similar to one another was novel. Both provided greater offloading than the shoe cast walker option. They also shared a functional difference to the shoe cast walker. Both the ankle-high and knee-high RCW fixated the ankle joint. They did so via rigid medial and lateral struts that ran along the ankle and were used to prevent ankle motion. In contrast, the shoe cast walker was lacking such struts and allowed normal plantarflexion and dorsiflexion at the ankle joint. Therefore, preventing normal heel-toe walking by locking the ankle joint is necessary to achieve maximum forefoot offloading with a cast walker.

While the necessity to immobilize the ankle joint was ascertained by this study, it did not identify a need for removable cast walkers to extend up the full length of the shank. The ankle-high cast walker that extended only slightly above the ankle provided similar offloading to the knee-high device that extended up to the lower portion of the knee. In the case of the specific two devices considered in this study (ankle-high: Equalizer Walker, Össur; knee-high: DH Offloading Walker, Össur), the ankle-high device was 20% lighter than the knee-high device. As individuals with DFU are physically deconditioned[50], this reduction in weight would be expected to facilitate gait and movement of DFU patients and may lead to improved device adherence. The exploratory kinematic outcomes in the present study tend to support this theory. The fact that participants walked significantly slower in the knee-high cast walker compared to standard shoes, however, did not walk significantly slower in the ankle-high cast walker suggests the participants were able to more easily ambulate in the ankle-high walker than the knee-high walker. Although the study was limited by simple straight-ahead walking trials with no obstacles or other challenges, a trend was identified in the centre of mass data that suggested potentially improved stability in the ankle-high walker relative to the knee-high device. However, the simple walking task and lack of a priori sample size estimation, prohibited the ability to make a conclusive determination as to whether the participants were more stable while walking in the ankle-high device relative to the knee-high device.

2.5: Publication 4

Decreasing an offloading device’s size and offsetting its imposed limb length discrepancy leads to improved comfort and gait (2018)

2.5.1: Publication 4 Aim

The aim of this study was to determine whether the size of removable cast walkers and limb length discrepancy they typically induce, negatively impact comfort and gait of diabetic individuals.

2.5.2: Publication 4 Summary

Twenty-five adults with diabetes (type 1=2; type 2=23) and at risk for DFU were recruited. In order to avoid the possibility of study activities causing a deterioration in an active DFU, individuals with an active DFU were excluded from participating. Participants were all able to walk without the need for an assistive device such as a cane or crutches. Additionally, none of the participants had previously received care for a limb length discrepancy. Each participant “completed walking trials under five different conditions: 1) bilateral standardized athletic shoes (New Balance, Boston, MA), 2) a standardized athletic shoe on one foot and an ankle-high RCW on the other foot, 3) a standardized athletic shoe plus an external shoe lift (Evenup LLC, Buford, GA) on one foot and an ankle-high RCW on the other foot, 4) a standardized athletic shoe on one foot and a knee-high RCW on the other foot, and 5) a standardized athletic shoe plus an external shoe lift on one foot and a knee-high RCW on the other foot" (p. 1401)[31].

During each 20m walking trial spatial/temporal parameters of gait (i.e. velocity, stance time, base of support) were captured by a 7.3m long instrumented carpet (GAITRite; CIR Systems Inc., Franklin, NJ) that was positioned in the middle of the walkway. Additionally, plantar pressure loading of the feet was captured by instrumented insoles (Pedar-X; Novel, München, Germany). Participants were asked to walk as they normally would during each trial and no effort was made to control speed between trials. Although variations in speed would be expected to alter foot pressures, the purpose of the study was to determine whether gait parameters changed under the varied footwear conditions. Following the completion of all of the walking trials, participants were asked to rate the comfort of each footwear condition via a visual analog scale.

Comfort data was analysed by a one-way (footwear condition) repeated measures ANOVA. The participants perceived significant differences in comfort ($p<0.005$; effect size = 0.30). Both of the offloading trials in which the lift was not used were less comfortable than the bilateral athletic shoes condition. Neither of the offloading conditions in which the external shoe lift was used significantly differed from the bilateral athletic shoes.

The gait and plantar pressure data collected in the four offloading conditions were normalized by the values collected in the bilateral athletic shoes condition. The normalized data was then assessed by a two-way (cast walker height x contralateral limb lift use) repeated measures ANOVA. Mean walking velocity was significantly reduced ($p=0.006$; effect size=0.27) with use of the knee-high cast walker. Use of the contralateral lift did not impact walking velocity. However, the use of the lift did impact variability in walking velocity (step-by-step). All offloading conditions had higher variability in walking velocity relative to athletic shoes, but the use of the lift resulted in significantly less variability than offloading trials in which the lift was not used. Cast walker height did not impact variability in step velocity. Stance time for the limb using the cast walker was significantly affected by lift use (p=.011; effect size=0.25) but not by the height of the cast walkers (p=.095). All offloading conditions had higher stance time for the offloaded limb than when walking in bilateral athletic shoes, however, the increase was smaller when the lift was used. Base of support for the limb using the cast walkers was not affected by walker height or contralateral limb lift use.

Numerous significant findings were found between footwear conditions in regards to the plantar pressure data. The use of the contralateral lift resulted in higher pressures in three of four forefoot regions assessed on the offloaded foot. The difference at the medial forefoot (1.6%) was non-significant but the differences at the intermediate forefoot (4.5%), lateral forefoot (5.6%) and hallux (3.6%) were significant. Similarly, the height of the cast walker significantly affected three of the four forefoot regions for the offloaded foot. The knee-high walker resulted in greater offloading at the medial forefoot (8.1%), intermediate forefoot (8.6%) and lateral forefoot (4.8%). For the non-offloaded limb, the use of the lift had an opposite effect to that seen on the offloaded limb. Use of the lift resulted in significantly reduced pressure throughout the forefoot of the foot using the lift (medial forefoot= 4.2%; intermediate forefoot= 7.6%; lateral forefoot= 11.9%; hallux= 6.3%). Cast walker height had no significant effect on forefoot loading for the non-offloaded limb.

2.5.3: Publication 4 New Knowledge Gained

Despite being considered the gold-standard for offloading DFU[55], knee-high irremovable devices (total contact casts and non-removable walkers) are not routinely used by clinicians[25-27]. Limited tolerance by patients is one of the reported reasons why knee-high irremovable devices are not more commonly utilized[25]. Limited tolerance also inhibits the benefit of removable offloading devices as multiple studies have found adherence with such devices to be low[29,34]. Publication 2 of this thesis identified self-reported instability as a predictor of non-adherence and this finding was confirmed by an additional study regarding reasons for non-adherence to self-care by people with DFU[56]. The substantial weight of knee-high devices and their imposition of an artificial limb length discrepancy are additional factors that may negatively influence offloading adherence[57]. Publication 4 sought to determine whether reducing a cast walker's size/weight and preventing it from causing a limb length discrepancy would positively impact the user experience by improving comfort and gait.

The varied offloading conditions did result in differences in perceived comfort as well as a number of gait parameters. The study participants reported the ankle-high cast walker paired with the contralateral lift as the most comfortable offloading condition and the comfort rating for this condition did not differ from that reported for walking in bilateral athletic shoes. The least comfortable offloading condition was the knee-high cast walker without a contralateral lift. A previous study[58] of custom-made footwear for preventing DFU reported comfort as the highest priority for patients when determining footwear usability, thus the comfort findings in the present study likely have implications for adherence levels with the varied offloading options. The current study's findings regarding gait parameters also have likely implications for adherence. Prior studies have noted older adults with diabetes walk with slower velocities as fear of falling increases[44,59]. Similarly, Reeves et al.[60] found gait velocity to be negatively correlated with self-perceived unsteadiness. Dingwell et al. postulated that reductions in walking speed by individuals with diabetic neuropathy are a compensatory strategy[61]. In addition to absolute walking speed, greater variability in speed has been found to be a discriminating factor between those older adults that do or do not fall[62]. Collectively this prior research suggests the gait velocity findings in the present study may be due to participants feeling more stable in the ankle-high cast walker with contralateral limb lift offloading condition. If that is the case, a corresponding increase in patient adherence would be expected if patients with active DFU were offloaded in this manner in contrast to patients provided with a knee-high cast walker without a contralateral limb lift.

While this study found comfort and gait parameters were improved with the ankle-high walker and contralateral limb lift condition, the greatest reduction in plantar pressure for the offloaded limb was noted in the knee-high walker without contralateral lift condition. As the study was not a prospective study of patients with active DFU, it was not possible to determine the ultimate impact of the varied offloading conditions on wound healing. However, it is postulated that if the ankle-high walker paired with a contralateral lift does lead to increased adherence in DFU patients, the increased adherence will outweigh the lesser amount of offloading provided by this offloading option. Future randomized controlled trials in patients with active DFU will be required to test this hypothesis.

Chapter 3: Monitoring and Managing Physical Activity Publications

3.1: Critical Account of Physical Activity Publications

This PhD thesis includes the first study to objectively quantify the amount of time individuals at risk for DFU spend standing[63]. The study associated with Publication 5 found that participants spent twice as much time standing each day as they did walking, thereby implying future studies and interventions regarding the association between DFU and PA should not be limited to solely tracking step counts. One of the surprising findings of the prior initial investigations that assessed the association between PA and DFUs was that patients at risk for DFU took the majority of their total daily steps inside of their homes[33]. This finding was made by merging step counts from a pedometer with self-report diaries of time spent away from home. Utilizing self-reports to capture places visited by patients in future investigations and interventions regarding the association between environment and PA engagement, poses the risk of both unintentional and intentional errors in reporting. This PhD thesis presents a publication that addresses this limitation[36]. Publication 6 reviews the development and application of a methodology for monitoring location-specific PA via pairing GPS data with accelerometry based PA data. The capacity to continuously and objectively monitor how PA patterns vary according to a person's environment will greatly aid future work addressing the association between weight-bearing activity and DFUs.

In addition to presenting work focused on improving the monitoring and quantification of PA engagement by those with or at risk for DFU, publications 7-9 of this thesis cover efforts to help these individuals appropriately manage their levels of weight-bearing PA. The European Association for the Study of Diabetes and the American Diabetes Association are in agreement that "…efforts to improve diet and exercise remain the foundation of all glycemic management (p. 26)"[64]. Although meeting activity guidelines is a common challenge throughout the entire population of persons with diabetes, those individuals at risk for diabetic foot ulcers (DFUs) are less likely to engage in PA, due in part to the unique barriers they report (e.g., distress about developing a DFU or needing an amputation)[65-67]. Patient and provider fears about DFU developing in association with efforts to increase weight-bearing PA are understandable in light of the fact that DFUs typically form in response to repetitive trauma produced by weight bearing PA[18,19]. However, in a departure from past guidelines, the most recent joint guidelines from the American Diabetes Association and the American College of Sports Medicine recognizes that *moderate* walking does not increase risk for DFU by individuals with peripheral neuropathy[68]. In fact, there is growing support in the literature for the belief that controlled increases in PA can reduce DFU risk[57,69-71].

Therefore there is a need for identifying means of safely improving PA profiles of persons at-risk for DFU. Although persons at-risk have commonly been excluded from exercise and PA interventional studies in the past[67], there have been some exercise studies done within this population[72-75]. While these limited past studies have shown potential benefits, the interventions they employed would be costly to widely implement both from fiscal and time perspectives as they relied on 1-6 in person visits per week and are generally not covered by insurance. In addition to often being cost prohibitive for large scale implementation, these supervised activity interventions have generally suffered from a lack of behaviour change strategies that may be necessary to promote maintenance.

Publication 7 of this thesis focused on the use of a technology-based (activity monitors and text messaging) PA intervention for individuals at-risk for DFU[37]. The intervention was intended to gradually increase participants' PA in order to improve their health without causing a DFU in response to the concerted effort to increase activity. This initial pilot study found participants had a small improvement in diabetes control (0.33% reduction in HbA1c; Cohen's d= 0.23) and a moderate increase in PA (882 steps/day; Cohen's d=0.66).

As alluded to when previously discussing this thesis' offloading studies, devices used to treat active DFU can make walking difficult. Furthermore, extra caution is warranted in considering how much load is acceptable for a foot with an active DFU. Past research has shown that high peak plantar pressures are associated with longer DFU healing times[76]. Even when gold standard offloading devices are provided to patients it is not clear how much upright weight bearing PA is appropriate for individuals with active DFU[77]. With this in mind, this thesis presents two studies regarding the evaluation of a cycling cleat that was designed to allow individuals with a forefoot DFU to participate in exercise incorporating the lower extremity without exposing the DFU to stress of sufficient magnitude to inhibit healing. The cleat was similar in design to a RCW and its interface with the bicycle was intended to limit foot loading to the heal region of the foot.

The first study of the cleat (Publication 8) included healthy participants and served to confirm that the cleat did significantly offload feet while cycling[38]. In progressing towards use by patients with active DFU, the second study (Publication 9) involved individuals at-risk for DFU[39]. In addition to confirming the offloading capacity of the cleat in a population more representative of patients with active DFU, this secondary study found increased perfusion to the distal portion of the foot following cycling with the cleat. This increased blood perfusion is important as it implies that use of the cleat may not only provide general exercise induced health benefits but may actually aid healing of DFU as blood perfusion to these wounds is often insufficient. One likely challenge to future large scale use of the device, is practical limitations of patients coming into clinical/physiotherapy settings for regular cycling sessions. Both Publication 8 and 9 were limited to evaluating the cleat in a highly controlled research environment in which research personnel assisted participants in their use of the cleat. Future work should consider means of feasibly implementing the cycling exercise safely in patients' homes.

3.2: Publication 5

The Importance of Time Spent Standing for those at Risk of Diabetic Foot Ulceration (2010)

3.2.1: Publication 5 Aim

This study sought to more comprehensively quantify weight bearing activity conducted by individuals at risk for DFU than had been previously possible. In addition to capturing the traditional metric of steps taken by participants, the duration of time spent standing, sitting and lying down was also measured.

3.2.2: Publication 5 Summary

Thirteen participants at risk for DFU (presenting with DPN) and a mean age of 59 ± 8 years were recruited. Neuropathic status was defined as the inability to detect a 10 gram Semms Weinstein Monofilament at one or more of the following locations: hallux, 1st metatarsal head, 3rd metatarsal head, and 5th metatarsal head[78]. Participants were given an undershirt that contained a padded pouch at a position corresponding to their sternum. The pouch held a novel triaxial accelerometer based activity monitor (PAMSys; BioSensics, Cambridge, MA USA) that was capable of continuously tracking body posture in addition to gait data[79]. Participants were asked to wear the undershirt and associated activity monitor continuously for 48 hours. They were advised to only take it off while bathing. Data was sampled continuously at 50Hz and periods when the undershirt and monitor were not worn were automatically identified during data processing by identifying periods of minimal acceleration amplitudes. Over the course of the 48hr monitoring period, participants only removed the undershirt and sensor for 17.5 ± 29.9min.

3.2.3: Publication 5 New Knowledge Gained

Prior to this study, objective investigations into PA profiles of individuals at risk for DFU were limited to measuring how many steps participants took[80,81]. This study found that participants spent 13.5 ± 5.3% of their time standing, 6.1 ±

3.1% walking, 37.3 ± 6.3% sitting, and 44.3 ± 8.1% lying down per day. Thus previous investigations concerned with mechanistically understanding how stresses applied to the feet during weight bearing activity lead to DFU, had likely failed to capture two-thirds of the participants' weight-bearing time by failing to measure standing time. In addition to being the first study to quantify how much time patients at risk for DFU spend standing (as well as sitting and lying down), it also provided a more detailed description of participants' walking profiles than was possible in prior studies. Statistics pertaining to individual bouts of walking were reported in Publication 5. The maximum duration walking bout for each participant was on average only 3.9 ± 3.8min, which equated to 422 ± 403 steps. Surprisingly, the correlation between participants' total number of steps per day and the duration of their longest continuous walking episode was not significant (r = 0.32, P = 0.30).

3.3: Publication 6

Monitoring Location Specific Physical Activity via Integration of Accelerometry and Geotechnology within Patients with or at-risk of Diabetic Foot Ulcers: A Technological Report (2017)

3.3.1: Publication 6 Aim

The project associated with the publication had two primary aims. The first was to develop a methodology for objectively collecting location-specific PA data within patients with or at-risk for DFU. Although underpowered to conclusively determine whether differences exited, the project secondarily sought to make preliminary comparisons of location-specific PA profiles of patients with DFU versus those at-risk.

3.3.2: Publication 6 Summary

Five participants at-risk for DFU (mean age= 55±11 years) and five with active DFU (mean age= 55±5 years) were recruited for the project. All participants were community dwelling and did not rely on a wheelchair or other such device for mobility. The at-risk participants were individuals at the highest possible risk for a future DFU, as they all had a prior history of DFU[82-84]. At the time of enrolment all at-risk participants had been ulcer free for ≥4 weeks. The participants with active DFU were all utilizing different offloading modalities at the time of participation. The list of modalities included: removable cast walker, diabetic shoe, wedge forefoot offloading shoe, soft cast paired with a walking boot and an accommodative surgical shoe.

Each participant was provided three devices to be used in monitoring their PA for 72hrs. They were each given the same triaxial accelerometer based activity monitor (PAMSys; BioSensics, Cambridge, MA USA) as was used in Publication 5 of this thesis. As in that prior study, participants were asked to wear the activity monitor at all times (including sleeping episodes) with the exception of bathing periods. Participants were also given a global positioning system (GPS) monitor (QStarz Travel recorder XT, Taipei, Taiwan). Participants were advised to wear the GPS monitor on a belt or to keep it in a pocket of their pants. Participants were also give a digital watch with a built in voice recorder. The watch had an alarm that was activated every two hours between 10:00 and 20:00 each day. Each time the alarm went off, participants were to use the watch's voice recorder to log where they were and their current PA status (ex. walking, standing, sitting, etc.).

The collected GPS data was processed using an algorithm with episode detection rules based on spatial density and GPS data was classified as stops (staypoints) and moves (trips)[85,86]. The time points at which stop and move episode began and ended were synchronized with the accelerometer's activity data. This synchronized GPS and activity data set was then compared to participants' self-reported daily logs using a custom LabVIEW 2015 program (National instruments, Austin, TX USA).

Across the subjects, the average proportion on the monitoring period for which the raw GPS data failed to provide a location was 13.1±20.4%. Once the GPS data was processed and synchronized with the PA data, a GPS location was only lacking for 1.5±2.1% of the 72hr monitoring period. After the self-reported location and activity logs from the digital watches were transcribed, it was found that 80±11% of the self-reported log entries had corresponding GPS locations. The agreement between self-reported and GPS identified locations were in agreement 98±6% of the time.

The participants with an active DFU participated in more weight bearing (standing and walking) PA at home than away from home (2.61±2.58 vs 0.91±0.51 hrs/day, Cohen's d = 1.1). The at-risk participants had a very similar amount of weight bearing activity in their homes (2.53±1.58 hrs/day) as did the participants with active DFU, however, at-risk participants had substantially more weight bearing activity outside of their homes (2.1±1.50 vs. 0.91±0.51 hrs/day, Cohen's d= 1.2).

3.3.3: Publication 6 New Knowledge Gained

No prior studies with a focus upon the diabetic foot have utilized methods integrating GPS provided location data with accelerometry-based PA data. Furthermore, although there have been PA studies of other populations that used GPS to monitor where PA was taking place, there was no consistent method of handling missing GPS data[87]. Thus these prior studies typically limited their focus to PA conducted outdoors where GPS signals are most easily captured[87-89]. Ignoring PA indoors would significantly limit the understanding of PA profiles of the diabetic foot population. This is due to the fact that prior research that relied on patients maintaining a diary of their location[33,90] (and the present study that objectively tracked participants' location) found individuals with diabetic foot complications engage in more PA within their homes than outside of their homes.

In addition to avoiding either unintentional or intentional errors in recall, the methods of the present project present another advantage over diary based methods of monitoring where PA occurs. By using GPS to objectively monitor where patients are engaging in PA the methods developed in this project, could help prevent user 'fatigue.' With diary methods, individuals must actively choose to log each trip and subsequent location they visit over the course of each day. This could be perceived as burdensome especially for long duration (several days) monitoring periods.

Another benefit of this project is the fact that it included participants at-risk for DFU and participants with active DFU. Both prior studies and current studies investigating PA and the diabetic foot tend to focus exclusively on either at-risk[33,65,90] patients or patients with active DFU[29,91,92]. Although the present project was limited by two small samples of participants, it did allow for some preliminary direct comparisons between at-risk and actively ulcerated individuals. As one might expect, the biggest difference between the two groups was the amount of PA undertaken outside of the home, with at-risk participants being more active away from home. However, both groups had more total weight bearing time inside of the home than outside of the home. The fact that all the participants with active DFU utilized different offloading devices could be seen as both a strength and a weakness. In common practice, providers use a wide variety of offloading options in treating patients[25,26]. Thus the inclusion of multiple devices in the present study tends to be representative of what happens in actual practice. However, it is likely that the different devices had varying effects on user's PA profiles and thus the varied offloading devices likely led to greater variability within the DFU participants than if a single device had been used by all participants. Appropriately scaled future studies will be able to delve into investigating this.

3.4: Publication 7

Feasibility of a low intensity, technology-based intervention for increasing PA in adults at risk for a diabetic foot ulcer: a mixed methods study (2019)

3.4.1: Publication 7 Aim

This study sought to conduct a feasibility assessment of a low-cost (from fiscal and personnel perspectives) PA intervention that utilized technology to help individuals at-risk for DFUs safely increase their activity levels.

3.4.2: Publication 7 Summary

Twelve participants (mean age= 60±9 years) were recruited to participate in the single arm investigation. Inclusion criteria included: type 1 or type 2 diabetes; sedentary status (<3 bouts of 20 minutes or more of PA/week[73]); age ≥ 21years; DPN associated loss of protective sensation as identified by Semmes Weinstein Monofilament[78] or vibration perception threshold[93]; HbA1c: 6.5-12.0%; primary care physician approval; and internet access. Exclusion criteria included: active DFU; proliferative retinopathy; pregnancy or planning to become pregnant; inability to participate in PA without assistance; peripheral vascular disease (ankle brachial index < 0.6); and cardiovascular autonomic neuropathy (resting heart rate > 100 bpm) or orthostatic hypotension)[94,95].

Following completion of the informed consent process, the screening visit began with confirming volunteers met all inclusion/exclusion criteria. Those that were found to be eligible completed assessments associated with the fabrication of custom made diabetic orthotics (TrueContour Therapeutic Insoles, Diapedia, State College, PA USA[96]). The orthotics and diabetic shoes were provided to all participants to lessen the likelihood of DFU formation over the course of the intervention. At the conclusion of the screening visit, participants were provided a GPS monitor (QStarz BT-Q1000XT, Taipei, Taiwan) and a triaxial PA monitor (PAMSys, BioSensics LLC, Newton, MA USA) to collect baseline location specific PA data for a one week period utilizing the methodology developed in association with Publication 6 of this thesis.

When participants returned for their next visit they were provided their custom insoles and diabetic shoes. They were also provided a secondary means of reducing the risk of developing a DFU while in the trial. Participants were given an infrared digital thermometer and asked to check daily for signs of preulcerative inflammation[97-100]. In addition to the thermometer they were given a diary instructing them to measure the temperature at six distinct locations on each foot and to determine the difference between corresponding sites on each foot. If the difference was >2.2°C (4°F) for any location, participants were to reduce their activity and call the study nurse. The last item given to participants at this visit was a personal commercial activity monitor (Fitbit Zip, San Francisco, CA USA). In order to remotely monitor participants' step counts, their devices were tied to a private online group to which the researchers had access.

The next four visits were used to implement the PA intervention. Each of the visits was approximately 45minutes in length and all four were to be completed within a two week window. The visits had four primary objectives: 1) initiate a personalized plan for increasing PA, 2) address PA concerns, 3) provision of education regarding PA behavioural strategies, and 4) provision of instruction for engaging in moderate intensity PA. A clinical psychologist met with participants to introduce the behavioural strategies that were based upon content of the Diabetes Prevention Program and were rooted in social cognitive and self-determination theories[101]. The moderate intensity PA consisted of walking on a treadmill at 40-70% of each participant's heart rate reserve and the duration of the first session walking bout was personalized to equate to approximately 50% of the participant's daily step count in the preceding week.

Following the four in person interventional visits, participants transitioned to an eight-week period of remote support. During this period participants were sent a new daily step count goal each week that was calculated based upon the step count for the previous week. A modest increase of 50 steps/day/week was used. Thus, if a participant averaged 5,000 steps/day in week 1, they would be asked to walk 5,050 steps/day in week 2. In order to avoid excessively large week to week increases, if a participant exceed their goal for a particular week by more than 15% their following week's goal would be capped at an increase of 15%. So for a participant with a 5,000 step/day goal that actually walked 6,000 steps/day, their goal for the following week would be 5,750 steps/day. In addition to the weekly step count goals, participants also received tailored text messages incorporating behavioural strategies to help them overcome PA barriers. Participants could also access the private Fitbit social network for the study and communicate with other participants. Research assistants also made daily posts on the network regarding behavioural strategies.

After the eight-week remote support period participants returned for a final study visit. In addition to repeating baseline measures, a key informant interview was conducted at the visit. The interviews were semi structured and focused on participants' perceptions regarding the intervention. Participants were also asked to rate the acceptability of the intervention using a modified version of the diabetes measurement and evaluation tool[102]. The tool had participants rate various aspects of the intervention on a scale of 1 (very dissatisfied) to 5 (very satisfied). Before leaving, participants were again provided the GPS monitor and triaxial PA monitor for monitoring location specific activity for one week.

Eleven of the twelve participants completed the final follow up visit and similarly only one participant failed to complete all four in person intervention visits (mean attendance rate = 97.9%). Responses across the valuation tool indicated high treatment acceptance with a mean of 4.79±0.24 across all items. Several items had a mean value of 5.0 (respect provided by your session leader; safety precautions taken during the sessions; ability of the session leader to provide interesting information; discussions about monitoring PA). The lowest scored item was ‘The convenience of the location’ for study visits (mean =4.18±1.08). During the interviews all participants reported the intervention was useful for increasing PA engagement. Additionally, 81% (9/11 participants) discussed benefits of setting goals and tracking PA. That same proportion of participants also identified benefits of accountability and encouragement in association with the text messages or the personal activity monitor (Fitbit Zip). Similar percentages of participants also found the safety measures of diabetic shoes/orthotics and temperature monitoring were beneficial.

The participants did report there was room for improvement with technological issues. These issues were generally relative to the personal physical activity monitor with 45% (5/11 participants) indicating they had some trouble syncing their monitor to their computer, tablet or phone. Another concern raised by 36% (4/11) of participants was a concern that the monitor did not always capture their activity. Two of the common barriers to PA discussed during the interviews were pain (63%, 7/11 participants) and weather (72%, 8/11 participants). Accordingly, the month participants began the intervention was found to influence changes in daily step counts over the course of the intervention.

Although this feasibility study was underpowered to make any definitive conclusions regarding efficacy of the intervention, positive trends were identified. Although the increases from week to week in step count goals were modest, participants went from 3825±1504 steps/day to 4707±1152. This equated to a medium effect size (d= 0.66). In addition to the change in step count a small improvement (*d*= 0.23) was seen in diabetes control with HbA1c values dropping from 8.47±1.34% at screening to 8.14±1.54% at end of study.

3.4.3: Publication 7 New Knowledge Gained

In contrast to past investigations, the present study evaluated the feasibility of a less intensive and technology dependent behavioural intervention to increase PA profiles of persons at risk-for DFU. Limiting the number of in person interventional visits to four proved to be manageable for participants as the average attendance rate for these visits was 97.9%. Furthermore, the technological intervention during the remote monitoring period was positively reviewed by the vast majority of participants. Although one prior PA intervention study in this population intentionally incorporated some behavioural change strategies[72], that study's strategies were limited to the use of social cognitive theory. That theory proposes that the interplay of personal, behavioural and environmental determinants influence health behaviours like PA[103]. A weakness of social cognitive theory is its limited attention to types of motivation[104-106]. The present study benefitted by incorporating strategies rooted in both social cognitive theory and self-determination theory[107]. The self-determination theory strategies focused on enhancing intrinsic motivation for PA and targeted use of extrinsic motivators. Lastly the novel interventional program in the present study was the first to incorporate two key DFU prevention methods (plantar tissue temperature monitoring and plantar pressure optimized diabetic orthotics) to maximize participant safety during the intervention.

3.5: Publication 8

CLEAR Cleat: A Proof of Concept Trial of an Aerobic Activity Facilitator to Reduce Plantar Forefoot Pressures and the Potential in Those with Foot Ulcers (2008)

3.5.1: Publication 8 Aim

This study sought to serve as the initial proof-of-concept regarding a specialized cycling cleat that was intended to offload the forefoot of users. The experimental cleat (CLEAR-Cleat[108]) was developed for the purpose of affording individuals with forefoot DFU the capacity to safely engage in lower extremity exercise.

3.5.2: Publication 8 Summary

Ten young (aged 23.7±1.3 years) participants without any history of chronic medical conditions, such as diabetes or cardiopulmonary disease, were recruited. Participants each completed one study visit at a human performance laboratory. During the visit participants completed stationary recumbent bicycle trials with their dominant foot placed in three different footwear conditions: 1) standard bicycle cleat (Lifecycle 9500R; Life Fitness, Schiller Park, Illinois USA) and an athletic shoe; 2) CLEAR-Cleat and an athletic shoe; 3) CLEAR-Cleat and an offloading insole (DH Walker Insole, Össur, Reykjavík, Iceland). The order of the footwear conditions was randomized for each participant. The non-dominant foot utilized the standard bicycle cleat in tandem with an athletic shoe for all trials. The CLEAR-Cleat was similar to a removable cast walker and included rigid struts extending up from the ankle region that allowed for fixation of the ankle at 90 degrees by a series of hook and loop straps (Figure 1). The cleat differed from cast walkers in that it was truncated at the midfoot. The cleat was attached to the bicycle's crank arm so that the heel was placed directly above the spindle, thus the

Figure 1. CLEAR-Cleat

forefoot extended out anteriorly beyond the cleat-bicycle interface.

The resistance level of the stationary cycle was held consistent for each participant across the different footwear conditions. During a preliminary warm-up period participants were asked to identify a comfortable resistance and cadence. During the subsequent cycling trials participants were asked to keep their rotations per minute (RPM) within a range of ±2 of their 'preferred cadence.' Each study trial consisted of cycling for seven minutes in the assigned footwear condition. In order to assess the offloading of the foot, plantar pressure insoles (Pedar-X, Novel, Munich, Germany) were used to collect foot loading data for the final 10 seconds of each minute of cycling. Plantar pressure data was collected bilaterally and was captured at 50Hz sampling frequency. Additionally, participants' heart rate and cycling RPM were recorded once per minute. Heart rate was to be used as a measure of exertion while the RPM values were to be used to confirm whether the workload was consistent across conditions.

Variables analyzed from the plantar pressure insole data included peak pressure, pressure-time integral and contact area. Masking software (Novel, Munich, Germany) was used to determine these variables' values at the following regions of interest: forefoot (distal 47% of foot), rearfoot (proximal 53% of foot) and total foot. Mean values for each 10 second collection of loading data were used for statistical analyses. A repeated measures ANOVA was conducted for each region for each variable. The ANOVA included main effects of: foot (dominant/CLEAR Cleat foot vs non-dominant/control foot), footwear condition, and time (minutes 1-7). Tukey's Honestly Significant Difference test was used for post hoc analyses of main effects and interactions that were found to be significant.

The plantar pressure insole data indicated the CLEAR Cleat significantly (p-values for all of the following offloading differences discussed were <0.01) offloaded the forefoot. When focusing on the foot that utilized the cleat, the contact area of the forefoot significantly decreased in a stepwise progression in going from athletic shoes paired with the bicycle's standard cleat, to the athletic shoes paired with the CLEAR Cleat, to the offloading insole paired with the CLEAR Cleat. These changes in forefoot contact area drove similar significant differences in total foot contact area for the foot using the cleat. Although the contact area for the forefoot and total foot of the CLEAR Cleat foot changed, the contact area for the rearfoot did not significantly differ between the different footwear conditions. Both the peak pressure and pressure-time integral data for the forefoot mimicked the contact area outcomes. Namely the offloading insole paired with CLEAR Cleat resulted in the least forefoot pressure, followed by the athletic shoe paired with the CLEAR Cleat, followed by the athletic shoe paired with the bicycle's standard cleat. Although the contact area of the rearfoot remained consistent across the conditions, the peak pressure and pressure-time integral values did change. Both variables yielded their highest values in the athletic shoe paired with the CLEAR-Cleat, followed by the offloading insole paired with the CLEAR-Cleat, and the athletic shoe paired with the standard bicycle cleat.

The RPM did not differ significantly between the athletic shoe paired with the standard cleat (82±13), athletic shoe paired with the CLEAR Cleat (81±13) and the offloading insole paired with the CLEAR Cleat (81±12). Since the resistance level was fixed across conditions, the lack of difference in RPM indicates the participants were exercising at a consistent workload across conditions. Similarly to RPM, the percentage of age-predicted maximum heart rate maintained while cycling did not differ across footwear conditions (athletic shoes & standard cleat= 60.9±3.0%; athletic shoe & CLEAR Cleat= 60.4±1.8%; offloading insole & CLEAR Cleat = 61.1±3.6%). The heart rate data suggest the cycling efficiency of participants did not change across conditions.

3.5.3: Publication 8 New Knowledge Gained

This thesis has already discussed the importance of PA to managing diabetes and the fact that individuals at risk for DFU typically engage in insufficient amounts of PA. Although extra caution to ensure healing is feasible when considering individuals with active DFU, it is still a major concern that individuals with active DFU have been objectively shown to be even more sedentary than at-risk individuals[109]. This is not a transient concern, as people with a history of DFU also self-report more sedentary behaviours than other cohorts of individuals with diabetes[65]. The study associated with publication 8 provided initial support for a means to allow persons with active DFU to safely exercise. The study was able to demonstrate initial proof-of-concept regarding the ability to utilize a modified cycling interface to reduce physical stress to the forefoot during stationary cycling exercise. This reduction was stable throughout the seven minute cycling bout. Furthermore, the heart rate data indicates the CLEAR Cleat did not make it more challenging for participants to cycle.

3.6: Publication 9

Preliminary Evaluation of a Cycling Cleat Designed for Diabetic Foot Ulcers (2017)

3.6.1: Publication 9 Aim

Having demonstrated initial proof-of-concept of the CLEAR Cleat in healthy individuals within Publication 8, this study sought to confirm repeatability of those results in a group more representative of the population the cleat was designed for. In order to progress cautiously, Publication 9 involved individuals at-risk for DFU as opposed to individuals with active DFU. In addition to confirming the offloading functionality of the cleat, Publication 9's study also assessed the foot's thermal and vascular responses to cycling with the CLEAR Cleat. Previous animal and human studies of aged and obese populations have provided data suggesting exercise may aid in wound healing[110-112]. Increasing the temperature[113,114] of the foot and the blood perfusion[115,116] to the foot are two ways cycling could conceivably promote DFU healing.

3.6.2: Publication 9 Summary

The study included fifteen adults with diabetes and that were at grade 1 or higher risk for developing a DFU according to the International Working Group on the Diabetic Foot's risk classification system[15]. Potential participants were excluded if they presently (or within the past 4 weeks) had an active DFU or if they were being treated for any chronic cardiovascular condition such as coronary heart disease or chronic obstructive pulmonary disease. A sample size estimate with power of 80 and $\alpha = 0.05$ using peak pressure data from an offloading study by Lavery et al.[46] (expected mean difference between cycling conditions 40kPa and standard deviation of 20kPa) suggested 7 participants would be needed to confirm the cleat offloaded participants' feet. However, in order to explore the secondary outcomes of thermal and vascular responses to cycling, the sample size was set to 15 participants.

Within a single study visit each participant completed two 5-minute trials using the same stationary recumbent cycle as used in Publication 8. In a randomized order across participants, one trial was done while cycling with bicycle's standard pedals in tandem with standardized athletic shoes (New Balance, Boston, MA USA).

During the other cycling trial the right foot used the CLEAR Cleat in combination with the same offloading insole used in Publication 8 (DH Walker Insole, Össur, Reykjavík, Iceland). During each participants' first trial they were asked to identify a resistance level and cadence (RPM) they would feel comfortable maintaining for 30 minutes. They then used the same resistance and target cadence for cycling in the second trial. Participants were given approximately 20 minutes to rest between the two trials.

As in Publication 8, plantar pressure insoles (Pedar-X; Novel, Munich, Germany) were used to compare peak pressure and pressure-time integral values between the two cycling conditions. Pressure data was collected at 100 Hz. Mean values for 10 consecutive revolutions near the end of each trial were utilized for analyses. Masking software (MultiMask, Novel) was used to determine pressure values at the following distinct regions of the foot: heel (proximal 30% of foot), midfoot (intermediate 30% of foot) and forefoot (distal 40% of foot).

Data for the secondary outcomes of thermal and vascular responses to cycling were collected prior to initiating each cycling trial and immediately after concluding each trial. Thermal response of the plantar aspect of the foot to cycling was assessed via infrared photography (Fluke; Everett, WA USA). SmartView 3.0 software (Fluke) was used in combination with a custom Matlab (MathWorks Inc, Natick, Massachusetts USA) code[117] to process the thermal images. Using the same definitions as were used with the plantar pressure data, the infrared foot images were divided into heel, midfoot and forefoot regions. The vascular response to cycling was assessed via laser Doppler perfusion monitoring (Transonic Systems Inc, Ithaca, NY USA). The flowprobe was attached to the plantar surface of the hallux prior to and at the conclusion of each cycling trial. It was attached via an adhesive sticker and an outline of sticker placement was made with a marker to ensure consistent placement of the probe for each measurement. Each perfusion measurement was approximately 1 minute in duration.

All data analyses were limited to the right foot (the foot that utilized the CLEAR Cleat in one of the two trials). Repeated measures ANOVA with main effects of foot region and footwear condition were used to analyse the peak pressure and pressure-time integral data sets. Footwear condition and the interaction of footwear condition with foot region were found to be significant for both pressure outcomes. Paired t-tests were used to look at the effect of footwear within each foot region. Peak pressure and pressure-time integral outcomes were similar. The values were significantly ($p < 0.05$) reduced in the forefoot and significantly increased in the heel while cycling with the CLEAR Cleat. Values at the midfoot did not differ between cycling conditions. A repeated measures ANOVA with main effects of time (pre versus post cycling) and footwear condition was used to assess the tissue perfusion data. Only the main effect of time was found to be significant with hallux perfusion increasing 73.9% (4.0 ± 1.2 versus 6.9 ± 1.4 tissue perfusion units) over the course of trials. Paired t-tests of pre versus post cycling temperature values and a repeated measures ANOVA for temperature change values with main effects of foot region and footwear condition did not find any significant differences in temperature values.

3.6.3: Publication 9 New Knowledge Gained

This study demonstrated the CLEAR Cleat was able to offload the forefoot of individuals closely matching the population for which it was primarily intended to be used. The pressure data indicate the cleat resulted in transferring pressure from the forefoot to the rear foot of individuals at-risk for DFU. Thus a patient with an active forefoot DFU should be able to exercise using the cleat without putting excessive stress on the DFU. The peak pressure applied to the forefoot (10 kPa) while cycling with the CLEAR Cleat was well below values observed while walking in offloading devices (66-134 kPA)[30,118].

In addition to suggesting cycling with the cleat would be safe for a forefoot DFU, the study also suggested such exercise might aid DFU healing. The noted increased microcirculation to the hallux suggests the excise may be able to increase oxygen and nutrient delivery to a forefoot DFU[119]. Increased microcirculation could also lead to improved inflammatory responses at a DFU site. Prior research in older mice has suggested an exercise induced anti-inflammatory response may improve wound healing[120]. Increased/prolonged inflammation inhibits DFU healing[121-123] and the anti-inflammatory cytokine IL-6 increases following exercise[124,125]. In addition to producing IL-6, skeletal muscles release it into the blood stream when contracting[124]. Thus cycling with the CLEAR Cleat may lead to reductions in excessive inflammation at DFU sites. One limitation in interpreting the perfusion results of the study is the fact that no clinical assessments of peripheral arterial disease were completed on participants. Thus it is unknown how the perfusion results might vary in individuals of differing levels of peripheral arterial disease.

The study associated with Publication 8 failed to demonstrate any potential thermotherapeutic benefit of cycling with the CLEAR Cleat. Prior studies have indicated externally warming the foot may aid DFU healing[113,114]. The present study failed to identify any changes in foot temperature following the cycling bouts, therefore it provided no support to the premise that cycling could aid DFU healing by acting to increase the temperature of the foot. However, it is possible future studies may find conflicting results. The present study was limited to fairly short bouts of 5 minutes and a mean heart rate of 105 beats per minutes after cycling suggests participants were exercising at a modest exertion level. It's possible that changes in foot temperature could be elicited in future studies if the cycling bouts are longer or participants engage in a higher exertion level.

Chapter 4: Falls in Individuals at Risk for Diabetic Foot Ulcer Publications

4.1: Critical Account of Falls Publications

The final set of publications associated with this thesis centre on the problem of falls by patients with or at risk for DFU. Fear of falling and injuries caused by a fall can significantly limit individuals' PA levels. Publication 10 of this thesis is a review publication that provides perspective on: the scope of the problem in older adults with diabetes, diabetes associated factors that predispose individuals to falling, and interventions to reduce individuals' risk for falling[42]. Some of the risk factors include decreased sensorimotor function, musculoskeletal deficiencies, pain, and therapeutic footwear (particularly devices used to offload active DFU).

DPN is a key diabetic foot disease risk-factor for falling[43]. Up to 50% of persons with diabetes will eventually develop signs and symptoms of DPN[126]. In their seminal 1999 paper investigating DFU risk factors, Boyko et al. found sensory neuropathy was a highly significant predictor of DFU and noted it was unfortunately not reversible[14]. Unfortunately, identification of an effective and reliable means of reversing loss of protective sensation remains elusive. Despite referencing the importance of screening for loss of protective sensation, the American Diabetes Association's 2018 compendium regarding diagnosing and managing diabetic foot complications makes no reference to treatment options for improving protective sensation[127]. Preliminary results regarding an intervention that was intended to treat sensory neuropathy are presented within Publication 11 of this thesis[43].

Publication 11's randomized controlled trial investigated the use of electrical stimulation therapy on plantar sensation and postural control of patients with DPN.

This study differed from prior studies that had used low level electrical[128-130] or mechanical[131] stimulation as low-level noise to 'boost' previously unperceivable external stimuli to the point where the external stimuli were recognized by sensory neurons. The study associated with Publication 11 sought to determine whether routine provision of an electrical stimulation therapy would result in benefits that persisted in the absence of active stimulation. There were some mixed results in regards to the sensation outcomes of vibration perception threshold testing and Semmes-Weinstein monofilament testing which were assessed in all 54 study participants. The assessment of changes in postural control was a secondary exploratory outcome and was only measured in a subset of 13 participants. Despite being an exploratory outcome, a statistically significant improvement in postural control was noted in association with the electrical stimulation therapy. This improved postural control indicated the therapy might help reduce fall risk in patients with DPN by improving peripheral nerve function. However, additional studies with sufficiently long follow up periods to identify whether fall rates decline are required to validate this hypothesis.

Publication 12 is the final falls related publication within this thesis and it dealt with the potential impact of DPN upon patients' fear of falling[44]. As referenced throughout the current chapter, DPN is a risk factor for falls. While falls can result in immediate physical harm to the body, fear of falling can also be problematic. A 'healthy' concern for falling could lead individuals to adapt strategies intended to reduce their likelihood of falling, however, such fear can also result in a number of deleterious outcomes. Anxiety, social withdrawal and restrictions in PA are all associated with concern for falling[132-136]. Decreasing PA engagement may only serve to compound the actual risk of falling by resulting in physical deconditioning that would limit individuals' capacity to recover from challenges to their balance. Publication 12 reports findings of a study that assessed the association of DPN with fear of falling as well as whether fear of falling in this sample of individuals was associated with a number of gait parameters. To date, research in this area remains minimal. Publication 12's results indicated that although older adults with diabetes were generally fearful of falling, the fear did not appear to be associated with severity of DPN. However, multiple gait parameters were significantly associated with fear of falling. The study concluded that fear of falling may be an unreliable indicator of fall risk.

One limitation of Publication 12 was its reliance on a single clinical assessment (vibration perception threshold) of peripheral neuropathy. Although nerve conduction velocity is considered the gold standard for diagnosing DPN, it is expensive, time consuming and often necessitates an additional clinic visit for patients[137]. The American Diabetes Association's Standards of Medical Care in Diabetes recommends sensation be tested as part of an annual physical examination of diabetic patients via Semmes Weinstein 10-g monofilament testing and a secondary test of either vibration, temperature or pinprick sensation[138]. Thus the use of vibration perception threshold testing in Publication 12 is well aligned with established standards of care, however, the study would have benefited from secondarily assessing participants' sensation via Semmes Weinstein Monofilament.

4.2: Publication 10

A Growing Troubling Triad: Diabetes, Aging, and Falls (2013)

4.2.1: Publication 10 Aim

This review publication served to inform readers about factors that predispose individuals with diabetes to experience falls. It also discussed the severity of falls within this population as well as means to mitigate falls within this vulnerable population.

4.2.2: Publication 10 Summary

The introduction for Publication 10 began by reviewing the scope of the growing problem of falls within aging populations of western nations. This included the annual cost of treating falls at the turn of the 21st century in the United Kingdom (£981/$1.9 billion US)[139], Australia ($86.4 million/$66.1 million US)[140] and the United States ($19.2 billion US)[141]. In order to establish the scale of the problem within persons with diabetes, the annual incidence statistics for falls in persons with diabetes over 65 years old (39%)[142] and persons over 55 years old (35%)[143] were reported. In addition to providing the incidence numbers, Publication 10 noted the fact that individuals with diabetes are at higher risk for falls than those without diabetes[144,145]

Publication 10 proceeded to review a number of factors that predispose persons with diabetes to experience falls. The first risk factors to be discussed centred on neurological and musculoskeletal matters. Individuals with diminished plantar sensation within their feet due to DPN have been found to have increased postural sway and reduced postural control[63,146]. Furthermore, a study of over 9,000 older women found that DPN and postural instability were the most important factors in explaining the relationship between diabetes and falls[145]. Reduced PA and muscle strength have also been identified as contributing to altered gait patterns and an increased risk for falling by individuals with diabetes[147,148]. Diminished plantar flexion strength specifically, has been linked to increased centre of mass displacement which in turn results in decreased maximum forward reach distance in patients with diabetes[149]. Thus it is not surprising that Macgilchrist et al. found ambulatory patients with diabetes whom were fallers had 40% less ankle plantar flexion strength than non-fallers[143]. Additionally, older persons with diabetes and reduced muscle strength have been found to adopt slower walking speeds and increase the duration of their double support phase while walking which is likely in response to their increased instability[150,151].

The association of foot/body pain and pharmacological complications with falls were reviewed next. Foot pain has been demonstrated to be a fall risk-factor in the broader population of community dwelling older adults[152,153]. Unfortunately, in addition to losing the capacity to sense what should be painful stimuli, persons with diabetes are prone to developing peripheral neuropathic pain which occurs conversely in the absence of painful stimuli[137]. In addition to this pain increasing fall risk, the treatment of the pain may also increase risk. Peripheral neuropathic pain is commonly treated with psychotropic medications and these medications have been found to increase the risk for experiencing a fall[147,154]. In addition to psychotropic medications, the total number of medications persons with diabetes are taking are a concern relative to falls. Older adults with diabetes are prone to taking more prescription medications than their peers[147] and patients with diabetes begin to have a heightened risk for falling when taking four or more prescription medications[155].

The last risk factor for falls by persons with diabetes to be reviewed was offloading footwear. As discussed throughout Chapter 2 of this thesis, reduced stability is a major concern in association with the provision of devices used to treat diabetic foot ulcers. This is most evident in devices such as total contact casts and cast walkers used to treat active diabetic foot ulcers[156]. Normal gait and standing balance can both be challenged by these devices. Some key reasons include the fixation of the ankle joint, the inclusion of a rocker bottom sole and inducement of a limb length discrepancy. Findings from Publication 2 of this thesis further illuminated the relationship between ulcer offloading devices and balance by finding that self-reported postural instability was negatively associated with offloading device adherence[29]. Although to a lesser magnitude, footwear used to prevent diabetic foot ulcers may also contribute to reduced stability. Rocker bottom soles may also be incorporated into preventative footwear and their convex design provides a smaller base of support to the foot. Additionally, insoles that achieve their goal of reducing peak pressures may at the same time be reducing stability. Such insoles increase contact area across the surface of the foot and transfer some load away from high stress areas such as the metatarsal heads to lower stress areas. Van Deursen postulated reducing peak pressures and increasing contact area could either diminish or improve stability[156]. He suggested it may result in greater cutaneous feedback through the recruitment of a greater number of sensory neurons. Conversely he noted that by reducing peak pressures across the foot, such insoles may decrease the likelihood of patients' compromised neurons from registering foot loading (i.e. few neurons would receive a stimulus of sufficient magnitude to be detected). Paton et al. appeared to provide support to the latter option in a study of patients with DPN that were assessed while wearing varied insole designs[157]. They found that stability was diminished in insoles with arch fill that would serve to offload the forefoot by transferring some load to the midfoot.

After reviewing risk factors for falls, Publication 10 discussed the heightened risk for poor outcomes following a fall by persons with diabetes. Unfortunately, individuals with diabetes are at an increased risk of incurring a fracture in association with a fall[158,159]. The increased risk for fractures by older adults with diabetes have been found to be associated with altered body composition, retinopathy, peripheral and autonomic neuropathy, hypoglycaemia and use of medications (particularly thiazolidinediones)[160,161]. In addition to the heightened risk of experiencing a fracture, persons with diabetes are also prone to poorer recoveries in association with fractures. Following a hip fracture; persons with diabetes have been found to have a worse length of stay efficiency in the hospital (measure of recovery per day in the hospital)[162], worse functional outcome following rehabilitation[163], and poorer health-related quality of life[158].

The final section of Publication 10 discussed means to reduce fall-risk within persons with diabetes. The publication primarily reviewed the results of studies investigating traditional strength, gait and balance training programs. There is good evidence that these interventions can reduce fall-risk within diabetic individuals[151,164-166]. The fact that such results have been found within the specific population of persons with DPN is especially encouraging[151,164,165]. Furthermore one study that compared diabetic individuals with a history of falling with three other groups (diabetic individuals with no history of falling, non-diabetic individuals with a history of falling and non-diabetic individuals without a history of falling) found the greatest improvements from their intervention were elicited in the diabetic individuals with a history of falling[164].

Unfortunately, at the time of the drafting of Publication 10 there was not much evidence regarding the capacity of strength, gait and balance training to reduce actual falls. Studies designed to look at fall risk factors such as balance generally require smaller samples and shorter follow-up durations than studies seeking to assess whether an intervention has reduced actual fall occurrence. Confirming that an intervention has actually reduced falls requires a large enough sample to ensure enough events occur in the control condition in order to identify whether a clinically meaningful reduction has been achieved in the intervention group. However, Publication 10 did discuss one study regarding the introduction of a strength and balance intervention for persons with DPN that did report falls data[167]. This study identified no difference in falls between participants randomized to the intervention and a control group, however, there are several key limitations in the study that should be kept in mind. Falls were not a primary outcome in the design of the study from which the data came. The 2010 publication by Kruse et al. was a secondary analysis of data from a study focused on confirming whether an exercise intervention would increase PA engagement by participants. Additionally there are compliance concerns within the study's intervention group that may have contributed to the finding by the authors that "the intervention was insufficient to improve strength and balance in this population."

4.2.3: Publication 10 New Knowledge Gained

This single publication serves to educate clinicians, researchers and policy makers on: the scale of the problem of falls within persons with diabetes, the factors that predispose them to falling and means to combat diabetes related falls. Due to the high number of falls, high likelihood of sustaining a serious fall injury and a worse prognosis for recovery; much more work is needed to reduce the fall related burden upon older persons with diabetes. The impact of Publication 10 can in part be appreciated by the high number of times it has been cited since its publication in October of 2013 (76 times as of 3rd of July 2020 according to Google Scholar).

4.3: Publication 11

A Novel Plantar Stimulation Technology for Improving Protective Sensation and Postural Control in Patients With Diabetic Peripheral Neuropathy- A Double-Blinded, Randomized Study (2013)

4.3.1: Publication 11 Aim

The primary aim of Publication 11 was to evaluate the effect of an electrical stimulation therapy upon plantar sensation in patients with DPN. The effect of the therapy upon participants' postural control was a secondary outcome that was explored in a subset of study participants.

4.3.2: Publication 11 Summary

Fifty-four patients from four clinical centres were randomized to receive either an active electrical stimulator for the feet or a sham device (active n=25; sham n=29). Inclusion criteria included a prior diagnosis of type 1 or type 2 diabetes and the presence of moderate DPN as defined by the inability to detect a 10g monofilament at between 1-3 sites out of 4 sites tested (hallux, 1st, 3rd, and 5th metatarsal heads)[78]. Exclusion criteria included peripheral arterial disease, active diabetic foot ulcer, medical conditions sensitive to electrical disturbance (ex. implanted electrical device or epilepsy), and the inability to walk 100ft.

The stimulation was provided while the feet rested in a footbath with a separate well for each foot. Each well had to two electrode plates that were connected to an electrical stimulator. The stimulation to the feet was transmitted to the feet via an aqueous solution in the footbath. Patients were instructed to gradually increase the stimulator's power at the start of each treatment session until they could either feel a comfortable tingling sensation or they reached 40% power (however, none of the patients felt the stimulation prior to reaching 40%). The stimulator provided 120Hz pulsed waveform current up to a maximum of 50mA. Participants in the sham group received a stimulator that was exactly the same in appearance to the one used by participants in the active group, however, it provided no stimulation to the feet. Participants completed five 30-minute treatment sessions per week for 6 weeks.

The primary outcome of plantar foot sensation was evaluated by two assessments. Monofilament testing was conducted at the same 4 sites on each foot as was done for screening, however, each site was tested 3 times with each of the following grades of monofilament: 2, 4, 6, 8, 10 and 15g. This resulted in a score of 0-72 for each foot. In addition to the extensive monofilament testing, vibration perception threshold was evaluated at the great toe using a biothesiometer[93,168]. After baseline testing, sensation was tested at week 2, 4 and 6 of the intervention. Sensation was also tested at a 6 week follow up visit for all subjects and at a 12 week follow up for a subset of 20 subjects.

In addition to the plantar sensation assessments, postural control was evaluated in a sub-sample of 13 participants (active n=5; sham n=8) from 2 of the study sites. Centre of mass (COM) sway served as the measure of postural control. COM sway was quantified using a 2 sensor system (BalanSens, Biosensics LLC, Cambridge, MA USA). Each sensor included a triaxial accelerometer, triaxial gyroscope and a triaxial magnetometer. One sensor was placed onto a participant’s shin and the other on the participant’s lower back. This allowed for the calculation of 3D angles of the hip and ankle during quiet standing, which in turn allowed for COM sway to be calculated in both the anterior-posterior and medial-lateral directions[63].

COM sway assessments were conducted in both eyes open and closed conditions for a standing duration of 30s in association with Romberg's protocol[169].

Change scores (i.e. baseline vs. week 2, week 4, week 6 or follow up) for the monofilament and VPT data were each analysed via a two-way (treatment group x visit) repeated-measures ANOVA. Significant ($p<0.05$) main effects or interactions were assessed by Sidak adjustment if more than two data groupings were compared or by independent t-tests if only two data groupings were to be compared. The main effect of visit was significant for the monofilament data with scores significantly improved at treatment weeks 4 and 6 as well as at the 6 week follow up visit. The monofilament data did not yield any significant findings in association with treatment group despite an apparent trend of a greater improvement in sensation within the active therapy group. In contrast, there was a significant interaction of treatment group and visit for the VPT data. At the visit following the 6th week of the intervention, the active therapy group had a significantly improved change in VPT (-9.6 ± 15.9V) relative to baseline in comparison to the sham therapy group (0.1 ± 19.5V). Although the active group still had better VPT scores at follow-up, the difference with the sham group was no longer significant.

A repeated-measures ANOVA was also used to assess the balance data. A few participants were unable to maintain their balance during the eyes-closed condition. As balance was a secondary outcome that was only assessed in 13 participants, the inability of some participants to complete the eyes-closed trials forced the investigators to focus exclusively on the eyes-open trials. There was no difference in COM sway between the groups at baseline. However, at week 2 of the intervention the active therapy group demonstrated a significant reduction in COM sway relative to baseline. This improvement in COM sway led to a significant between-group difference at week 2. This significant between-group difference in COM sway persisted throughout the rest of the intervention period as well as at the follow up visits 6 weeks and 12 weeks after the conclusion of the therapy.

4.3.3: Publication 11 New Knowledge Gained

This preliminary investigation of electrical stimulation therapy provided via an aqueous solution to treat DPN, provided initial data regarding impact of the therapy upon protective sensation and postural stability. Mixed outcomes were obtained with regards to the protective sensation measures. While the therapy was found to improve VPT scores, it was not shown to improve the monofilament scores. The monofilament scores were highly variable between subjects which contributed to the lack of between-group difference. It's possible that the high number of individual monofilament trials (72) per foot examined resulted in diminished concentration on the part of participants over the course of an exam. If this did occur it would have confounded the results and possibly contributed to the variability between participants. Even though the secondary outcome of postural control was limited to a small sample (active n=5; sham n=8), a statistically significant improvement was noted in the active therapy group relative to the sham therapy group.

The potential improvements in plantar sensation and balance indicate the electrical stimulation therapy may be able to reduce both diabetic foot ulcer risk as well as fall risk in patients with DPN. What set's this particular intervention apart from prior ones is the apparent lasting effect of the electrical stimulation therapy. As discussed earlier in this chapter, several prior studies had looked at the use of low-level electrical stimulation 'noise' to improve sensation by lowering the threshold required for an external stimulus to be perceived by the user[128-130]. However, an obvious limitation to such an approach is that under this paradigm a benefit is only provided while the individuals receive active stimulation. Such an approach would face many hurdles in successful implementation within the daily life of persons with DPN. In contrast, the electrical stimulation therapy evaluated in Publication 11 proved to be feasibly administered in participants' homes and provided a lasting benefit to nerve function beyond the period of active stimulation. Additional research is needed to confirm whether this approach is able to reduce the incidence of diabetic foot ulcers and falls.

4.4: Publication 12

Fear of falling is prevalent in older adults with Diabetes Mellitus but is unrelated to level of neuropathy (2013)

4.4.1: Publication 12 Aim

The aim of the study associated with Publication 12 was to assess whether DPN is associated with fear of falling with the aid of a validated measure for fear of falling. Secondarily, the study sought to determine whether DPN and fear of falling were associated with gait parameters indicative of increased risk for falling.

4.4.2: Publication 12 Summary

Thirty-four community dwelling participants with diabetes aged 45 years or older (mean 67.6±9.2) were recruited. Potential participants also needed to be able to walk further than 20m without the use of a walking aid. Exclusion criteria included neurological conditions (other than DPN) and orthopaedic conditions involving the lower extremities that might impact gait (ex. amputation or joint replacement).

Peripheral neuropathy was screened for via VPT values. A biothesiometer (Xilas Medical, San Antonio, Texas USA) was used to identify each participant's VPT (1-100V) at each hallux as described by Young et al.[170]. The mean of the left and right hallux VPT for each participant was used for analyses. Fear of falling was quantified by having participants complete the Falls Efficacy Scale International survey. This is a scale that was developed and validated by the Prevention of Falls Network Europe [171,172]. The sixteen item survey has a range of scores of 16 (no concern about falling) to 64 (severe concern about falling). Participants' gait was assessed with body worn inertial sensors[173,174] (LEGSys, BioSensics LLC, Cambridge, Massachusetts) while participants walked 20m at their preferred speed. The LEGSys system consists of 2 sensors placed on the shins, 2 placed on the thighs and one sensor on the lower back. Gait parameters captured included: stride velocity, stride length, stride time, double stance, intercycle gait speed variability and gait initiation (steps required to reach steady-state walking).

Using a cut point of 25V for VPT as previously described[170], 18 of the participants were classified as non-neuropathic (VPT=18.3±4.5V) and 16 were classified as neuropathic (VPT=49.7±21.9V). A stepwise linear regression model was used to assess which gait variables were independently associated with neuropathy level (VPT scores). Only those gait variables with a $p \leq 0.2$ in bivariate analyses were included in the multivariate analysis. Two gait parameters associated with stability, double support time and gait initiation steps, were positively associated with level of neuropathy. A secondary multivariate linear regression model was used to assess which variables were associated with fear of falling (FES-I scores). Despite the observed association for the gait parameters, no association was identified between peripheral neuropathy status and fear of falling.

4.4.3: Publication 12 New Knowledge Gained

Prior to Publication 12, the literature regarding DPN and fear of falling was extremely limited. There were, however, two publications that discussed an association between DPN and fear of falling. Powell et al. published a methodologically limited study that paired retrospectively collected clinical data regarding the use of phototherapy for DPN with a non-validated survey pertaining to history and fear of falling[175]. Without providing clarity in the improvement, the authors indicate all patients in the assessed cohort experienced improved sensation following the phototherapy. The authors also reported with a lack of clarity that patients in the cohort experienced a significant and 'substantial' reduction in neuropathic pain. After retrospectively collecting neuropathy data from patient charts both prior to and after initiation of the phototherapy, the authors contacted the patients by telephone a single time. They asked patients about their fall history and fear of falling before and after initiating the phototherapy. The patients reported a reduced incidence and fear of falling after initiating phototherapy. In another study that failed to use a validated fear of falling questionnaire and reported on painful DPN, Lalli et al.[176] found painful DPN was associated greater fear of falling and gait alterations indicative of increased risk of falling.

The results of Publication 12 provide further evidence of the association between DPN induced loss of protective sensation and heightened fall risk. Surprisingly, the study failed to identify a relationship between the clinical measure of loss of protective sensation and fear of falling. This secondary finding suggests patients with reduced sensation due to DPN may not fully appreciate their own fall risk. Although fear of falling was not tied to VPT scores, it is worth noting that across the entire sample fear of falling was highly prevalent. Eighty-two percent of participants were classified as either moderately or highly concerned about falling. Another possible interpretation of Publication 12's findings is that the gait adaptations found to be associated with neuropathy (ex. Increased double support time) served as compensatory strategies that mitigated an increased fear of falling in association with neuropathy.

Chapter 5: Future Work & Conclusions

5.1 Future Work

The 12 publications upon which this thesis is based represent a body of work that has made significant advances regarding three interrelated themes across DFU care: offloading, PA engagement and understanding the heightened risk of falls. This work has addressed important clinical questions. The addressment of those questions has in turn led to new questions and new avenues for pursuing scientific inquiry. The synergistic nature of the studies presented in this thesis allows them to collectively serve as building blocks for new studies. This chapter discusses one such ongoing project as well as several possible future lines of investigation.

Chapters 2-4 collectively laid out the case that postural instability and elevated falls risk contribute to non-adherence with offloading devices in patients with DPN. While the offloading publications 3 and 4 provided some preliminary insight into the impact of these devices on stability, the impact of such devices on stability was not a primary outcome[30,31]. Furthermore, these studies were limited to investigating stability during unchallenged indoor walking. Generally the ultimate cause of falls is the failure to appropriately compensate for a loss of balance during a more demanding task than simple walking over level ground[57]. A currently ongoing repeated measures study is seeking to determine whether the removable cast walker design features of walker height and imposed limb length discrepancy diminish compensatory responses to perturbations and therefore increase risk of falling. Within a single gait lab visit, participants are evaluated following waist-pull and treadmill imposed perturbations while wearing each of multiple offloading interventions. Interim results have already been presented at the 8th International Symposium on the Diabetic Foot[177]. The preliminary results presented suggest that smaller perturbations are required to elicit a protective step from individuals with DPN while wearing a knee-high walker with no contralateral lift in comparison to an ankle-high walker paired with a contralateral limb lift.

The findings of this ongoing lab-based offloading study are expected to provide further justification for a longitudinal randomized controlled trial in patients with active DFU. This would allow the investigation of whether prolonged use of different offloading devices lead to different adaptations by DFU patients over time. For example, it is hypothesized that adherence with a knee-high removable cast walker will decline more over time than adherence with an ankle-high removable cast walker.

Similarly, additional randomized controlled trials are anticipated to follow up other lines of investigation from this thesis. Publication 7 presented the results of a single arm PA intervention for persons at-risk for DFU. A future randomized controlled trial of longer duration than the original study is needed to confirm Publication 7's promising results. In addition to confirming the capacity of the intervention to impart meaningful user benefits, additional work is needed to evaluate the practicality of implementing the intervention in a clinical setting. The initial study was primarily carried out in the context of a research laboratory which cannot be replicated on the scale needed to benefit the millions of individuals at risk for DFU. The CLEAR Cleat results of this thesis' Publications 8 and 9 also provide sound justification for moving forward with a randomized controlled trial in patients with active DFU. Those two publications demonstrated the CLEAR Cleat will allow users to engage in exercise incorporating the lower extremities without concomitantly placing significant load on a DFU. In addition to determining whether prolonged use of the device elicits similar overall health benefits as other exercise interventions in persons with diabetes, future studies should assess whether regular use of the CLEAR Cleat results in a difference in the healing trajectory of active DFU.

5.2 Conclusions

DFU are an underappreciated yet massively burdensome malady. This thesis presents a substantial body of work pertaining to the three interrelated themes of offloading, monitoring and managing PA, and falls-risk in the context of persons with or at-risk for DFU. At its core, the collective work pertains to helping diabetic foot patients adapt healthier physical activity profiles.

Chapter 2 presented novel research that assessed offloading adherence and subsequent work to determine whether specific design features of removable cast walkers are likely to impact adherence[28-31]. Although current guidelines recommend knee-high walkers as the preferred first line choice[23], this thesis' work found ankle-high walkers yield similar offloading of the foot with greater comfort and reduced impact on users' mobility. Of the 12 publications upon which this thesis is based, Publication 4 is likely to have had the greatest immediate impact upon providers and patients. In addition to looking at the impact of different cast walker heights on gait and comfort, it also assessed how those outcome variables were impacted by the provision of a contralateral lift to offset cast walker induced limb length discrepancies. The outcomes of the study have direct relevance to clinicians' treatment regimens as the study results can help care providers in selecting the best offloading options for their patients. By jointly working with patients to take into account how offloading devices may impact gait and comfort, providers are likely to dispense offloading solutions that will offer the greatest likelihood for success for each patient.

The focus of Chapter 3 was PA and it began with two publications concerned with enhancing the means by which we quantify PA[35,36]. The first highlighted standing-time's substantial contribution to total daily weight bearing time in people with DPN[35]. The second presented methodology for pairing geospatial and PA data in order to appreciate the association between one's environment and level of PA[36]. The next set of Chapter 3 publications dealt with safely assisting individuals with diabetic foot disease become more physically active[37-39]. Of those three publications, Publication 7 has the greatest potential for immediately affecting clinical care. Although a larger randomized controlled trial is needed to confirm efficacy of the low-cost intervention for helping individuals at-risk for DFU to improve their physical activity profiles, a number of the study's interventional components can presently be implemented by care providers. For example, providers can discuss reasonable step count goals with patients. Then the providers can utilize electronic health records systems' patient portals (as an alternative to the text messaging used in the study) in order to maintain periodic contact regarding patients' successes and barriers in reaching their physical activity goals.

Chapter 4 concentrated on the association of the at-risk diabetic foot with accidental falls-risk, with the first publication reviewing the problem/evidence[42]. The following publication evaluated an electrical stimulation therapy to treat the fall-risk factor of DPN[43]. The final publication of the chapter (and thesis) presented a study that investigated the potential association between DPN and fear of falling[44]. Contrary to intuition, the study failed to identify an association between DPN and fear of falling. Collectively, the work encompassing this thesis has made inroads in mitigating the global burden of DFU and has also set the stage for further lines of investigation aimed towards increasing quality of life for those with diabetic foot disease.

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Appendix: Published Works Comprising Thesis

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