Title: Physiological and Psychological Challenges of Increasing Physical Activity and Exercise in Patients at Risk of Diabetic Foot Ulcers: A Critical Review

Short Title (up to 40 characters): Physical Activity and Foot Ulcers

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Abstract (250 max)

Obesity and a sedentary lifestyle are common challenges among individuals at risk of diabetic foot ulcers (DFUs). While substantial research exists on physical activity interventions in adults with diabetes, those at greatest risk for foot ulceration were often excluded or not well-represented. Both at-risk patients and their clinicians may be hesitant to increase physical activity due to their perception of DFU risks. Physical activity is not contraindicated for those at risk of DFU, yet patients at risk present with unique barriers to initiating increases in physical activity. This review focuses upon the physiological and psychological challenges of increasing physical activity and exercise in patients at risk of DFUs. Offloading, diabetic peripheral neuropathy, depression, pain, self-efficacy and social support, DFU risk-specific beliefs and emotions, and research to date on exercise interventions in this population are all discussed. Additionally, recommendations for implementing and researching physical activity interventions for individuals at risk for DFU are provided.

Keywords: offload, peripheral neuropathy, depression, self-efficacy, social support

Introduction

Obesity is tied to large decreases in life expectancy and large increases in lifetime healthcare costs for individuals with diabetes [1]. Individuals with diabetes having a body mass index (BMI) above a classification of “normal” are at increased risk of developing secondary complications of diabetes [2]. In particular obesity is highly prevalent in individuals with diabetic foot complications [3] and has been shown to be an independent predictor of diabetic foot ulcers (DFU) [4]. In addition to managing one’s diet, increased physical activity is a commonly prescribed means of combatting obesity and managing type 2 diabetes. Obesity is also highly prevalent in persons with type 1 diabetes [5] and an active lifestyle is associated with a better body composition profile [6]. Additionally, a recent meta-analysis regarding exercise and type 1 diabetes concluded there are insufficient well-designed studies to determine the effect of exercise on long term blood glucose control in persons with type 1 diabetes but current results are promising [7].

Physical activity interventions can include traditional exercise regimens or simply a concerted effort to increase one’s physical activity throughout the day (e.g. opting to takes stairs instead of an elevator). However, the high prevalence of sensory loss that places individuals with diabetes at risk for DFU and increases with age [8] eventually reaching up to 50% of older diabetic patients [9, 10], necessitates the need to consider DFU risk when making physical activity recommendations. DFU are the most important risk factor for lower extremity amputations in persons with diabetes [11], and individuals with diabetes are 15 to 46 times more likely to have lower extremity amputations than persons without diabetes, [12-15]. Eighty-four percent of these amputations are preceded by an ulceration [16] and individuals with diabetes face a 25% chance of developing a DFU within their lifetime [17].

While substantial research exists on regimented exercise interventions in adults with diabetes, those at greatest risk for foot ulceration are often excluded or not well-represented. Exercise is not contraindicated for those at risk [18, 19], yet patients at risk of diabetic foot ulceration present with unique physical and psychological barriers to initiating increases in physical activity and exercise. This review will focus upon the physical and psychological challenges of increasing physical activity and exercise in patients at risk of diabetic foot ulcers. A greater understanding of these challenges could stimulate research for developing interventions to safely increase exercise and physical activity in this vulnerable population. Specifically, this paper will review the following physical considerations: physical activity and the etiology of DFU, offloading, and sensory and motor impairments associated with diabetic peripheral neuropathy. Psychological considerations reviewed include: depression, pain, self-efficacy and social support, and diabetes and DFU risk-specific beliefs and emotions. Following a review of the challenges associated with increasing physical activity within this population, a review of exercise/physical activity studies performed to date in this population are reviewed. Lastly recommendations are made for implementing and researching exercise and physical activity in adults at risk for DFU.

Similarly to the joint position statement offered by the American College of Sports Medicine and the American Diabetes Association [18] regarding exercise within the broader population of people with Type 2 Diabetes, this article recognizes that many types of movement have implications for individuals at risk of DFU. Thus the broader term “physical activity” and more specific term of “exercise,” which refers to a subset of planned and structured physical activity performed with the intent of improving physical fitness, may generally be considered interchangeable within this article. At times where more specificity is required, terms such as “regimented exercise” or “daily physical activity level” will be used.

Physical considerations regarding exercise and physical activity

Physical Activity & Etiology of DFU

With progressive increases in BMI comes an increased risk of developing DFU relative to normal weight individuals. Morbidly obese (BMI≥40) women have a hazard ratio of 3.34 and men have a 4.97 hazard ratio of developing a DFU relative to normal weight individuals [2]. The etiology of DFU has important implications regarding exercise and physical activity patterns by those at risk of developing a DFU. Although DFU can form in response to acute trauma such as stepping on a sharp object, they typically form in response to repetitive trauma produced by weight bearing activity conducted by individuals with diabetic peripheral neuropathy [20, 21]. The pressure and shear stress applied to the surface of the foot as a result of physical activity lead to inflammation and eventually autolysis of the soft tissue beneath bony prominences of the foot [22, 23]. In considering the insensate foot, Paul Brand commonly referred to these individuals as lacking the “gift of pain” [24]. Whereas a person with healthy feet can adjust their gait and foot loading in reaction to pain from weight bearing activities, a person with diabetic peripheral neuropathy does not receive pain input, and thus continues applying high levels of physical stress to isolated areas of the foot allowing a DFU to form without any direct warning.

With this understanding of DFU etiology it would be logical to assume that the more active a person is, the greater their risk for forming a DFU. However, multiple prospective studies of at risk patients that tracked daily physical activity levels via objective instruments as well as self-report questionnaires, found that the individuals that ulcerated had lower physical activity levels than those that did not ulcerate [25, 26]. Similar results have been obtained in a cross-sectional study. Maluf and Mueller [27] paired laboratory measured plantar pressure data with accelerometer based daily step counts to calculate estimated daily cumulative stress to the feet of three groups. The groups consisted of 1) subjects with diagnosed diabetes mellitus and peripheral neuropathy and a history of recurrent ulcers, 2) subjects with diagnosed diabetes mellitus and peripheral neuropathy with no history of recurrent ulcers, and 3) non-diabetic control subjects. The subjects with diabetes and a history of recurrent ulcers accumulated significantly less (41%) cumulative plantar pressure than the subjects with diabetes and no history of ulcers. Additionally, the subjects with diabetes and no history of recurrent ulcers had an equivalent level of daily cumulative plantar pressure as controls. Thus the individuals applying the least cumulative plantar pressure to their feet were the ones who were developing ulcers.

A secondary finding in one of the prospective physical activity studies gives some insight into why it is the least active individuals that appear to be prone to DFU. Although the individuals that developed DFU in the Armstrong et al. study exhibited significantly less average daily physical activity than those that did not, the subjects that ulcerated did exhibit significantly greater daily variability in activity [25]. This difference in variability was further highlighted by the fact that in the two weeks prior to the development of ulcers the ulcerative group's daily variability increased even more (coefficient of variation =115.4 ± 43.0%), while the mean level of daily activity did not change. Although variability was not discussed by Maluf and Mueller [27], the coefficients of variability can be calculated using the means and standard deviations provided. In regards to daily cumulative forefoot pressure, the subjects with a history of recurrent DFU had a coefficient of variability of 63% whereas subjects with diabetic peripheral neuropathy and no history of DFU had a value of 42%. Although there is a good amount of support for the hypothesis that variability and not quantity of physical activity is the primary concern in regards to DFU, a recent study found a small but statistically significant (odds ratio 0.93 [95%CI: 0.89-0.99]) protective effect associated with greater day-to-day variation in stride count [28]. However, there are a number of factors that may help explain this discrepancy. Firstly, variability was based off a single seven day assessment of physical activity recorded within the study's 18 month protocol and the days preceding ulcers were not targeted for monitoring. Hence, variability immediately preceding ulceration was not known. Furthermore, although those subjects that ulcerated had a lower group mean variation in daily stride count than those that did not reulcerate (1068±549 vs. 1276±793 strides), the group that ulcerated also had a lower mean daily stride count (3,238±1,287 vs. 3,437±1,990 strides). Thus, as was the case in the other studies, those subjects that ulcerated tended to be less active than those that did not.

The concept that variability of activity is key in the etiology of DFU and that greater levels of average daily activity provide a protective effect, lends credence to the physical stress theory described by Mueller and Maluf [29]. According to the theory there are five tissue responses to physical stress (Figure 1). The initial stage of decreased stress tolerance is associated with minimal physical stress (physical activity) and the subsequent stages are associated with progressively higher physical stress levels. Stages two through five include: maintenance, increased stress tolerance, injury, and death. This theory provides a conceptual basis for why people with generally low levels of physical activity are more likely to ulcerate than those with higher routine physical activity levels. Individuals that typically have low levels of activity will have deconditioned the stress tolerance of the plantar skin of their feet. Thus their skin is not able to tolerate the stress when they are exposed to a sudden isolated episode of increased physical activity. Previous studies [25-27] therefore show that it is not simply a case of greater levels of plantar foot loading giving rise to an increased ulceration risk. In contrast, it seems to be due to the actual nature of foot loading in the presence of certain complications of diabetes such as peripheral neuropathy. More specifically, sudden increases in foot loading by patients might be a key mechanism to explain the risk of developing a DFU [30], rather than the absolute volume of foot loading.

Offloading

Offloading refers to the redistribution away from or minimization of physical stress from sites of the foot that are exposed to excessive loading during weight bearing activity. In addition to the standard bony prominences found in healthy feet; foot deformities, limited joint mobility and partial foot amputations can produce additional sites of concentrated pressure and shear stress on the feet of diabetic individuals [31-33] . Specialized offloading footwear are prescribed to protect both feet at risk of DFU as well as those that have an active DFU [34].

For feet at risk of DFU, custom molded insoles (orthoses) are recommended in order to provide maximum protection to the feet by accommodating foot deformities/prominences and minimizing the physical stress applied to them [35]. Footwear with molded insoles have been shown to significantly reduce plantar pressure on the foot (offload), however, a 2008 systematic review [34] indicated the capacity for footwear to prevent DFU still required rigorous investigation. Traditionally orthoses have been designed based upon foot shape and clinician recommendations, although some recent investigations have begun to evaluate the incorporation of objective assessments of foot loading into the design and/or modification of orthoses [36, 37]. These two studies have provided some of the best data to date regarding the use of orthoses for the prevention of DFU. Both studies focused on prevention of secondary DFU. Ulbrecht et al. found that orthoses based both on foot shape and barefoot walking plantar pressure profiles, resulted in a reduction of submetatarsal head DFU recurrence in contrast to orthoses based solely on foot shape [36]. In a similar concept, Bus et al. [37] utilized inshoe plantar pressure assessments to modify shape based orthoses in an effort to improve the insoles. Bus et al. also found a benefit to plantar pressure optimized insoles, however, a reduction in DFU recurrence was only evident when limiting the analysis to subjects with high orthoses adherence levels (≥80% of steps taken while wearing orthoses).

A recent investigation of patients that had been provided custom-made footwear for preventing secondary DFU found that despite patients generally having a positive perception of the usability of the footwear, their self-reported adherence was low [38]. Fifty-eight percent of participants reported wearing their footwear <60% of waking hours. Perceived benefit of the footwear was the only assessed potential determinant of adherence that was found to be a significant predictor of adherence. The same group had previously published data regarding objectively measured adherence to custom-made footwear for DFU prevention and found on average the footwear was worn for 71 ± 25% of steps taken per day [39]. In that study lower BMI, more severe foot deformity and more appealing footwear were significantly associated with higher adherence. Knowles and Boulton [40] also previously concluded the appearance of preventative footwear is important for adherence, particularly in respect to female patients.

Adherent use is also an important concept in considering devices designed for offloading active DFUs [41]. Healing DFUs typically requires a greater level of offloading than can be provided by footwear that is provided for the prevention of DFUs. A recent systematic review indicated that non-removable, pressure-relieving casts are the most effective means for healing plantar DFUs [42]. Although total contact casts are considered as the gold standard in DFU offloading [6], removable cast walkers are far more commonly used [43-45]. The offloading provided by removable cast walkers has been shown to be as good if not better than total contact casts [31, 46, 47]; however, they are associated with poorer healing [47, 48]. Poor adherence with removable cast walkers has been assumed to be the reason for the discrepancy. The initial study to objectively evaluate this adherence found it to be particularly low with an average of only 28% of daily steps being taken while subjects wore their walkers [49]. More recently a direct association has been demonstrated between adherence to removable offloading devices and DFU healing [50]. The weight of the devices, their imposed modification of gait and their negative impact on balance all likely contribute to low levels of adherence [51, 52]. Considering the necessity to appropriately offload active DFU and the challenges in doing so, attempts to increase physical activity levels in individuals with active DFUs should focus on activities with minimal or ideally no weight bearing at the site of the wound [53].

Sensory and motor impairments associated with diabetic peripheral neuropathy

In line with risk stratification guidelines, diabetes patients considered at high risk for DFU will almost exclusively have peripheral neuropathy [54, 55]. Sensory deficits associated with diabetic peripheral neuropathy are well known [56] and should be an important factor when considering the challenges and barriers to modifying physical activity levels in diabetes patients at high risk for DFU. Perhaps less well acknowledged, however, is the fact that diabetic peripheral neuropathy is also associated with muscle weakness and atrophy [57-59], which have implications for motor control that should also be taken into consideration for engagement with physical activity regimens. In the diabetic foot at high-risk for DFU, sensory deficits will impact upon the patient’s ability to detect and respond appropriately to ground contact during walking and other everyday ambulatory activities. It has been shown that this sensory deficit, together with impairments to motor control associated with diabetic peripheral neuropathy impairs joint stability [60] and compromises balance control [61] in patients with diabetic peripheral neuropathy.

Although extremely difficult to completely separate the effects of sensory and motor impairments on unsteadiness in patients with diabetic neuropathy and at high-risk for DFU, motor aspects of gait have been shown to be reduced/impaired in both patients with diabetic neuropathy and patients with diabetes but without neuropathy [60-62]. However, the finding that balance is only compromised in patients with diabetic neuropathy and not in diabetes patients without peripheral neuropathy [61], may point towards the importance of sensory deficits for causing balance impairments during every day gait tasks. The implications of this are that engaging in weight-bearing ambulatory activities places the diabetic patient with a high-risk for DFU at risk of sustaining a fall. Patients with diabetic neuropathy are at a much greater risk of falling compared to their aged-matched counterparts without diabetes for the reasons outlined above [63, 64]. Level over ground walking may be considered one of the 'safer' forms of physical activity for diabetic patients at high-risk for DFU, in comparison with more 'challenging' forms such as walking on uneven surfaces [65] and stair walking [60, 61]. This is explained by the greater physical demands of these more challenging activities combined with the more complex sensory requirements, both of which present a problem for patients at high-risk for DFU with sensory and motor impairments. High-load resistance exercise training performed once a week for 16 weeks has recently been shown to be effective for increasing the speed of strength development around lower limb joints in patients with diabetic neuropathy when walking on stairs [66]. Since patients with diabetic neuropathy are known to have a slower speed of strength development, which may be a contributory factor to falling [60], the outcome of this intervention is expected to reduce the risk of falling in patients at high risk for DFU. Resistance exercise training can also be considered a relatively safe form of exercise for patients at high risk for DFU since it involves no forces on the sole of the foot for some exercises (e.g., leg extension exercise) and for other exercises (e.g., leg press) although high forces are applied to the sole of the foot they last only very briefly (~30 seconds). Another advantage of this type of exercise (resistance training) is the improvement of muscle strength, which can help to better prepare patients at high risk for DFU for the more sustained demands of exercise requiring muscular endurance such as treadmill or cycle exercise.

Psychological challenges and barriers to exercise and physical activity

Most of the literature examining psychological barriers to and facilitators of exercise in adults with diabetes do not focus on those at risk for a DFU. However, a fair amount is known about the psyche of individuals either at risk or with an active DFU. Therefore, the potential for psychological commonalities within that population to serve as barriers and facilitators of physical activity are discussed with support from literature pertaining to the broader population of adults with diabetes, and where possible, relevant studies of adults with DFU are integrated.

Depression and Exercise in Adults with Diabetes

There is consistent evidence that the prevalence of clinical depression and elevated depressive symptoms are higher among people with diabetes than among the general population. Meta-analyses report that the risk of depression in diabetic patients is twice that of adults without diabetes, regardless of the method used to measure depression [67, 68]. The prevalence of adults with diabetes having major depression is 11-27%, and women with diabetes are 2-3 times more likely to have depression than men with diabetes [67-69].

The elevated incidence of depression and depressive symptoms is concerning as depression is a barrier to exercise among adults with diabetes. A bidirectional relationship exists between depression and physical activity among adults with diabetes; those who meet criteria for depression or have elevated depressive symptoms are significantly more likely to be physically inactive, and those who are physically inactive are more likely to meet criteria for depression or have elevated depressive symptoms [70-76]. While the majority of the evidence is cross-sectional, a 5-year longitudinal study of patients with diabetes found that those who experienced persistent or worsening depressive symptoms were less likely to engage in regular exercise [77].

Among adults with diabetes, several possible mechanisms may explain the relationship between depression and physical inactivity. Symptoms of depression like anhedonia (i.e., lack of interest or pleasure), low energy and hypersomnia can be incompatible with exercise. These symptoms could directly undermine motivation for exercise, as well as influence other behaviors and strategies that assist with exercise initiation and maintenance. For example, depressive symptoms among individuals with diabetes are associated with less use of relapse prevention behaviors, less ability to restructure plans for exercise, greater perception of barriers relative to benefits of exercise and lower self-efficacy for exercise [78]. For adults with diabetes, depression may compound the typical exercise barriers reported (e.g., lack of time, weather), making an exercise regimen seem insurmountable.

Depression and Diabetic Foot Ulceration

Several studies have examined the relationship between depression and advanced diabetic complications over time. A longitudinal investigation of 4623 primary care patients with type

2 diabetes showed that major depressive disorder was associated with an increased risk of advanced micro- and macrovascular complications over the ensuing 5 years [79]. These included blindness, end-stage renal disease and amputations, as well as myocardial infarction, stroke, cardiovascular procedures and death. More recently, several prospective studies have convincingly demonstrated the link between depressive symptoms and the risk of an initial DFU [80-82].

In contrast to studies linking depression to an increased DFU risk, research on the relationship between DFU and the risk for depression has produced conflicting results. One study that used a structured clinical interview to diagnose depression found no differences in major depression over the past year between adults with and without a DFU [83]. Though no differences in major depression may exist, adults with a current DFU report more depressive symptoms compared to their counterparts without a foot ulcer [84] and compared to those at risk for a foot ulcer [85]. Interestingly, one cross-sectional study found no differences in depressive symptoms between those with and without a DFU on a valid, self-report measure of depression, although adults with a DFU were more likely to rate themselves as depressed on a single item measure [86].

Conflicting evidence for the relationship between depressive symptoms among those with a DFU could be attributed to differences in pain experiences. The cross-sectional results of the study by Vileikyte et al. (2005) demonstrated that neuropathic symptoms of pain, unsteadiness and reduced feeling in the feet symptoms, and associated psychosocial factors accounted for nearly half of the variance in depression symptoms [87]. The longitudinal findings of Vileikyte et al. (2009) were largely consistent with the cross-sectional observations and demonstrated that while neuropathic pain contributed to depression, perceived unsteadiness and its psychosocial consequences dominated this relationship over time [88]. The emergence of unsteadiness as the symptom that is most strongly associated with depression warrants attention, especially as it has been recently demonstrated to predict non-adherence to offloading in patients with active DFU, which has significant implications for physical activity [89]. Somewhat unexpectedly, neither the presence of prior nor active DFUs were independently associated with depression in these reports, an observation that was corroborated by a large epidemiologic investigation [90]. Nonetheless, even though DFU are not independently associated with depression, they serve as a marker for an increased risk for elevated depressive symptoms, and DFU patients should be carefully monitored to determine whether they are depressed, especially in the light of findings linking depressive disorders to increased mortality in this patient population [91].

Pain

Pain is common among adults with diabetes. Musculoskeletal pain is 1.7 – 2.1 times more common in patients with diabetes compared to their counterparts without diabetes (Molsted 2012). Roughly 10-28% of adults with diabetic neuropathy, which increases risk for a DFU, experience neuropathic pain [92-94]. Neuropathic pain is often unaffected by medication, consistent and worse in the evening, making it a particularly troubling experience for patients with diabetes. Pain is also associated with depression in patients with diabetic neuropathy [87, 95], and increases in pain predict increases in depression over an 18-month period [88]. The relationship between pain and depression may magnify challenges to initiate exercise in this population. Musculoskeletal pain and neuropathic pain are common exercise barriers reported by adults with diabetes [96-99].

Despite the fact that pain may be a barrier to exercise in patients with diabetes, initial evidence suggests that exercise may actually alleviate pain. Three small pilot studies examined the impact of supervised exercise on pain in adults with diabetes. One study found that a single session of isometric exercise (i.e., exercise that involves the contraction of specific muscles) decreased pain during and following exercise in adults with diabetes [100]. The other pilot examined the impact of a 10-week individually tailored aerobic exercise and strength training intervention on pain in adults with peripheral neuropathy. Participants who completed at least 75% of the sessions experienced significant reductions in pain and neuropathic symptoms from baseline to post-intervention [101]. A 16-week aerobic exercise intervention for adults with painful peripheral neuropathy found that the program reduced participant's perception that pain interfered with their life, but had no impact on pain severity [102]. Small sample sizes and lack of a control group or long-term follow-up preclude recommending exercise to alleviate pain in patients with diabetes.

Facilitators: self-efficacy and social support

Self-efficacy is a common facilitator of physical activity generally, and in adults with diabetes. In adults with diabetes, cross-sectional studies support the association between self-efficacy for physical activity and greater physical activity [103, 104]. One small longitudinal study of adults with diabetes demonstrated that physical activity self-efficacy predicted greater physical activity six months later [104]. The influence of diabetes management self-efficacy (i.e., confidence in one's ability to engage in behaviors such as managing diet, checking blood glucose and physical activity) on engagement in physical activity is less clear. While one study of adults with diabetes and low socio-economic status found a positive relationship between diabetes management self-efficacy and physical activity engagement [105], diabetes management self-efficacy was not associated with physical activity in a sample of African-American and Hispanic adults with diabetes [106]. Since diabetes management self-efficacy encompasses more than just physical activity behavior, it may be a weaker predictor of physical activity.

Unfortunately, adults with diabetes report less physical activity self-efficacy compared to those without diabetes [107, 108]. However, two small pilot intervention studies provide initial support for strategies to improve self-efficacy and physical activity. A 10-week, patient-centered, shared-decision making intervention culturally tailored to African-Americans with diabetes increased diabetes management self-efficacy from baseline to the 10- week and 3 month follow-ups; self-reported participation in a physical activity program also increased from baseline to the 6-month follow-up [109]. In adults at risk for a DFU, a 3 session, knowledge-based intervention that focused on teaching proper foot care, including foot and leg exercise, facilitated increases in self-efficacy for all foot care behaviors, including exercise, from baseline to the 3-month follow-up [110]. Though neither study conducted a formal mediation assessment, increases in exercise self-efficacy resulting from the intervention may have contributed to increased exercise.

Like self-efficacy, social support is a key facilitator of physical activity engagement generally, and initial evidence supports it influence in adults with diabetes. Greater social support was associated with more engagement in diabetes self-care behaviors [111]. Though exercise was just one of six self-care behaviors examined, results are consistent with other studies that find positive associations between social support and exercise [112, 113]. In addition to facilitating physical activity, social support may also buffer adults with diabetes from experiencing psychological distress. A cross-sectional study of adults with diabetes found that frequent contact with friends was associated with less psychological distress [113]. Interestingly, neither living with a partner, nor frequent contact with family influenced psychological distress, which is consistent with a cross-sectional study of African-American and Hispanic adults with diabetes, which found no relationship between family support and physical activity [106]. The type of support provided by friends, versus what is provided by family, may be more integral to tempering emotional distress. If psychological distress interferes with exercise, friend support may be a stronger factor in promoting exercise, both directly by encouraging exercise, and indirectly by alleviating distress.

Diabetes and DFU risk-specific beliefs and emotions

Initial evidence suggests that diabetes-risk specific feelings may interfere with exercise in adults with diabetes. Fear of hyperglycemia is a frequently endorsed barrier to exercise among adults with type 1 diabetes [114, 115]. In a cross-sectional study of adults with diabetes, structural equation analyses demonstrated that greater diabetes-related distress was associated with less engagement in diabetes self-care behaviors, such as maintaining a healthy diet, exercise and foot care [105]. Exercise was just one of six self-care behaviors examined, but results are consistent with other studies that find negative associations between diabetes-related distress and exercise among adults with diabetes.

Mounting evidence points to the importance of DFU risk-specific cognitions and emotional responses in shaping foot self-care, which is critical to exercising safely and for the prevention and early detection of sores or ulcers [18]. Both cross-sectional [116] and longitudinal [117] investigations have shown that patient common-sense misconceptions about the nature of DFU risk and accompanying emotions of anger directed at health care providers hinder foot self-care. In contrast, better understanding about the pathways to DFU and worry about an amputation appear to promote foot self-care actions. These findings were corroborated in several patient populations at high risk for developing DFU [118, 119].

Among those diagnosed with a DFU, limitations resulting from the DFU may inhibit exercise and promote psychological distress. Adults with a newly diagnosed DFU reported that the inability to stand or walk was the most important factor in self-reported problems with anxiety and depression, self-care, and usual activities [120]. Mobility restrictions resulting from a DFU may contribute to current psychological distress and increase risk for future DFUs. Despite awareness of recommendations to ease back into activities after a healed foot ulcer, patients with a previous DFU reported a tendency to resume daily activities without delay or restriction, due to the frustration of having to limit activities while their ulcer healed [121]. Despite the benefits of increasing physical activity, a rapid, rather than gradual return to daily activities may increase risk of another DFU. Strategies for increasing physical activity in those with healed DFUs must encourage physical activity, while minimizing the risk of another DFU. These strategies should provide education on the risk of increased physical activity without promoting anxiety that would increase the desire to remain sedentary.

Taken together, it would appear that psycho-educational interventions aimed at enhancing physical activity in patients at high risk for developing DFU should address both psychological barriers to exercise, as well as DFU-risk specific emotional and cognitive responses shaping adherence to foot self-care.

Research to date on exercise

General review of exercise/physical activity in diabetics

Despite the substantial benefits of exercise, only 31-37% of adults with diabetes [122, 123] and 25% of older adults with diabetes exercise at or above recommended levels [124]. Exercise engagement in adults with diabetes is even lower when more objective measures of physical activity such as accelerometry are used [125]. Some evidence suggests that adults with type 1 diabetes engage in more exercise compared to those with type 2 diabetes [126, 127]. Women with diabetes report even less engagement in exercise than their male counterparts [124, 125, 128]. Furthermore, individuals with diabetes are more likely to relapse to a sedentary lifestyle after beginning an exercise program.[129] These low rates of exercise occur despite the fact that physicians are more likely to recommend exercise to patients with diabetes than to patients with cardiovascular disease, cancer or hypertension [130]. Although participation levels are low, substantial evidence supports the ability of exercise interventions to improve diabetes control [131, 132]. Moreover, leisure time physical activity has been shown to effectively cut the cost of care for type 2 diabetes [133].

Review of exercise/physical activity in at risk patients

The majority of individuals with diabetes that intentionally increase physical activity do so by engaging in walking, light jogging and other non-weight bearing activities. While weight bearing exercise would not be recommended for patients with open DFU[53], increases in weight bearing physical activity can be prescribed for patients at risk of DFU. Table 1 gives a comprehensive description of exercise intervention studies in the past 7 years that included patients with the key DFU risk factor of diabetic peripheral neuropathy (DPN). All studies provided supervised exercise interventions, with intervention durations ranging from 8 weeks

[134] to 12 months [135]. These studies found significant improvements in physical activity without increasing the risk of ulceration. Adverse events reported were either not significant or had no direct associations with the exercise interventions [101, 135, 136], suggesting supervised weight bearing exercise interventions are feasible in people with diabetic peripheral neuropathy. Treadmills were the most widely used equipment for weight bearing activities while stationary bicycles were used for non-weight bearing activities. All aerobic exercises were conducted at a moderate intensity with levels ranging from 40% to 70% of heart rate reserve (HRR). The maximum heart rate capacity was either calculated based on their exercise treadmill test [137], utilizing cycle ergometers[138, 139] or based on predicted heart rate maximum [136]. The frequency of exercise was 3 times per week with an average duration of approximately 30 min across all studies.

Supervised moderate weight bearing aerobic activity improved activity and gait parameters in multiple studies after 12 weeks of intervention [136, 138, 139]. Aerobic and resistance training has been found to improve cutaneous regeneration and increased intraepidermal nerve fiber density in DPN patients [101, 137]. Progression of DPN symptoms were also found to reduce or halt with moderate intensity exercise training without causing adverse events [134]. The prospective studies to date on DPN patients indicate that when supervised, DPN subjects are capable of performing similar aerobic activities as non-neuropathic diabetic patients and derive benefit. However, due to the relatively short duration of these studies, the long term health and DFU implications of exercise within this population remain unknown.

Table 1: Exercise intervention studies for individuals with diabetic peripheral neuropathy.

Study	Year	Study type	Patients	Exercise							Results
				Equipment	Type	Frequency	Intensity	Duration	Period	Supervised by	
Handsaker et al. [66]	2016	RCT	13 DM/ 9 DPN/ 21 Con T1 & T2	Resistance machines	Lower extremity resistance training	1 time per week	Heavy resistance	60 min	16 weeks	Investigator	Improved speed of strength generation during ascending/ descending stairs
Singleton et al. [137]	2015	Prospective	35 DM/ 32 DPN T2	Treadmill	aerobic/ resistance	150 min/week	moderate 11 to 14 Borg Perceived Exertion scale	30 to 90 min	18 weeks	PhD trained Physical Therapist	improved cutaneous regeneration, increased intraepidermal nerve fiber density
Kluding et al. [138]	2015	Prospective	18 DPN T2	cycle ergometer, treadmills, recumbent steppers, elliptical trainers	aerobic	3 times per week	50 to 70% of VO2 reserve	30 to 50 min	16 weeks	Licensed health care professionals	Supervised aerobic exercise in DPN population is feasible
Morrison et al. [139]	2014	Prospective	21 DM/ 16 DPN T2	cycle ergometers, treadmills, elliptical strider	aerobic	3 times per week	Moderate @50% HRR; Vigorous @75% HRR	Moderate -45min Vigorous -30min	12 weeks	only for peak testing on cycle ergometer	gait velocity, step length increased significantly after intervention
Dixit et al. [134]	2014	RCT	87 DPN T2	Treadmill	aerobic	150-360 min/week	40 to 60% of HRR	variable	8 weeks	Investigator	progression of DPN was reduced in the intervention group without adverse events

Mueller et al. [136]	2013	RCT	29 DPN T2	Treadmill, resistance bands and stationary bicycle	aerobic	3 times per week	60 to 70% age predicted max HR	variable	12 weeks	Licensed Physical Therapist	Weight bearing group improved step count and 6 min walk distance compared to non-weight bearing. 13 lesions and 4 ulcers were observed, 3 in non-weight bearing group.
Kluding et al. [101]	2012	Prospective	17 DPN (T1 or T2 not reported)	Recumbent stepper, stationary bicycle, treadmill, resistance machines	Aerobic & strength training	3-4 times per week	Aerobic- moderate intensity that progressively increased over time Resistance- moderate perceived exertion	30-50 min	10 weeks	Study team w/ varied health professions training	Improvement in neuropathic symptoms and increased cutaneous nerve branching
LeMaster et al. [140]	2008	RCT	79 DPN T1 & T2	exercise ball, beach ball, activity monitor	Leg strengthening and Balance exercises AND self-monitored walking program	3 times per week	Leg strengthening and balance exercise increased each session	variable	12 months	Strength and balance exercises- Licensed Physical Therapist; walking program self-monitored	Weight bearing activity did not lead to significant increase in foot ulcers and resulted in increased step count in intervention group.

Note: Con = non-diabetic control participants; DM= non-neuropathic participants with diabetes mellitus; DPN = participants with diabetic peripheral neuropathy; HR= heart rate; HRR= heart rate reserve; RCT = randomized controlled trial; T1 = participants with type 1 diabetes mellitus; T2 = participants with type 2 diabetes mellitus

Recommendations for implementing and researching exercise and physical activity in adults at risk for a DFU

Exercise and physical activity interventions in individuals at risk of DFU should incorporate a gradual and controlled increase in activity in order to limit the probability of DFU occurrence. Based on the success of most studies, (Table 1) which incorporated planned physical activity at frequencies of 3 times or more per week, interventions should seek to modify activity levels at least 3 days per week initially. Gradual increases in physical activity amount and frequency should be recommended to avoid large day to day variability in activity [25, 27] and to attain the American Diabetes Association's recommendation of 150 minutes of moderate intensity physical activity per week [141]. For some highly sedentary adults at risk for a DFU, emphasizing reductions in sedentary activity, rather than increases in exercise, may be a more palatable and tempered approach to gradually increasing physical activity. Even low intensity physical activity has been shown to improve glucose variability in patients with type 1 diabetes [142]. Research is needed to understand how best to reduce sedentary activity in adults at risk for a DFU, and whether those interventions could transition from decreasing sedentary activity to increasing exercise. Appropriately sized shoes [143-145] and offloading insoles should be worn during physical activity. Based upon previous research, a proposed upper limit for peak pressure while walking with footwear on is 200kPa [28, 146]. Daily plantar foot temperature monitoring [147] may allow individuals at risk of DFU to identify if they are ramping up activity too quickly by detecting pre-ulcerative inflammation caused by the skin being exposed to more

Recommendations for Increasing Physical Activity

- Incorporate planned physical activity 3 or more days per week with a goal of reaching 150 minutes per week
- Appropriately sized shoes should be worn and if possible customized insoles should be worn as well
- Daily home monitoring of feet's temperature
- Avoid unsupervised activities that significantly challenge balance

stress than it can safely accept [29, 147]. Due to the heightened concern for falls by individuals with diabetes [148], activities that significantly challenge participants' stability should be avoided.

A systematic review of the literature comparing physical activity advice only versus structured exercise training in type 2 diabetics concluded that physical activity advice alone is only associated with lower HbA1c values when combined with dietary advice, whereas structured exercise training alone results in reduced HbA1c values [131]. However, it would be quite difficult from a practical and financial standpoint to broadly initiate routine structured exercise training with the large population of individuals at risk of DFU. Therefore, relatively low resource requiring behavioral strategies that incorporate now common technology such as text messaging, mobile apps and online social networks to increasing physical activity merit investigation. Use of behavioral strategies such as problem solving and goal setting could also address the general and exercise-specific barriers reported by adults at risk for a DFU. If randomized trials confirm the benefits of exercise on pain, future research is needed to determine the optimum type and dose of exercise, as well as ways to enhance exercise motivation when exercise may be counterintuitive to patients, given its association with pain. Another area worthy of investigation is the association of physical activity interventions and falls. Increased physical activity could lead to increased probability for falls; however, conversely increased physical activity may reduce fall risk by improving individuals' strength and balance. Lastly, because little information is available regarding the long term implications of increasing physical activity in people at risk of DFU, long term prospective studies are warranted to look at both the health and DFU implications.

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Conflicts of Interest

Author RTC is named on a US patent (US 8,105,257 B2) for an exercise device designed for individuals with active diabetic foot ulcers. A publication concerning this device was cited in this manuscript.

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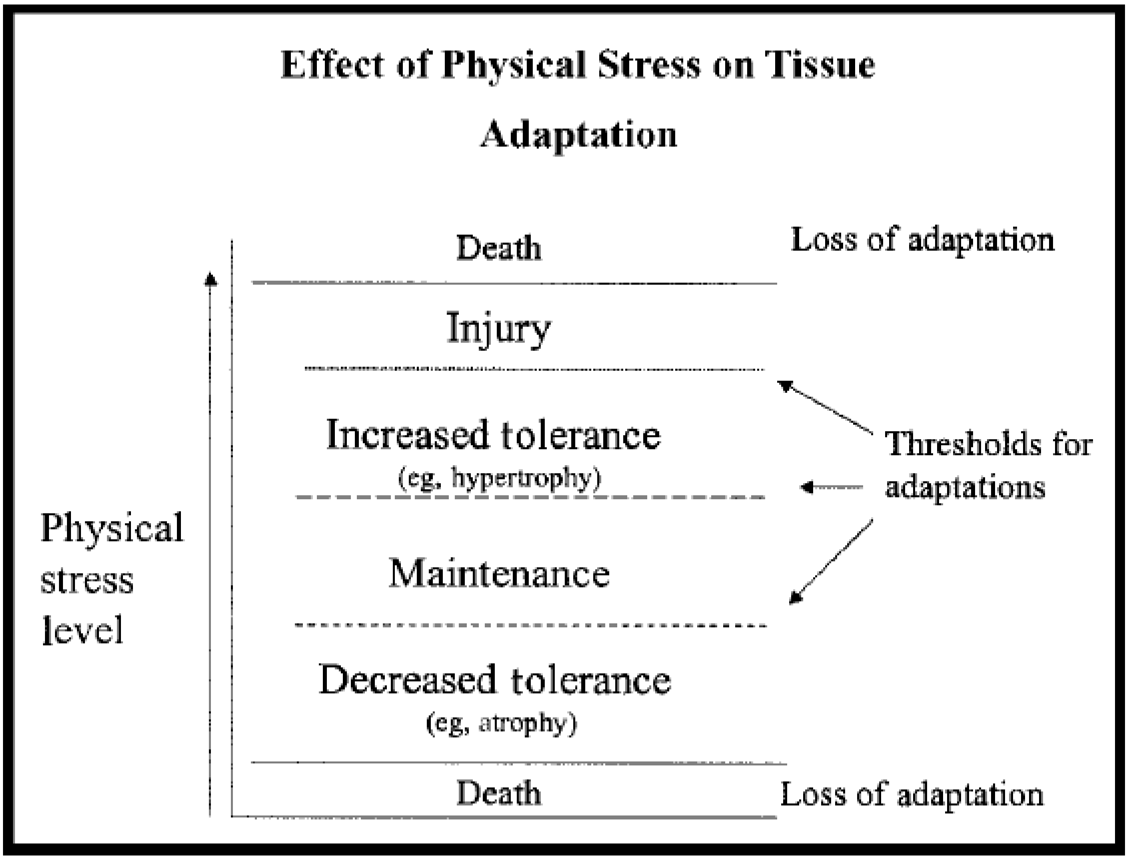

Figure 1. Effect of physical stress on tissue adaptation. Biological tissues exhibit 5 adaptive responses to physical stress. Each response is predicted to occur within a defined range along a continuum of stress levels. Specific thresholds define the upper and lower stress levels for each characteristic tissue response. The relative relationship between these thresholds is fairly consistent between people, whereas the absolute values for thresholds vary greatly. (Reprinted from *Phys Ther.* 2002; 82(4):383-403, with permission of the American Physical Therapy Association.)