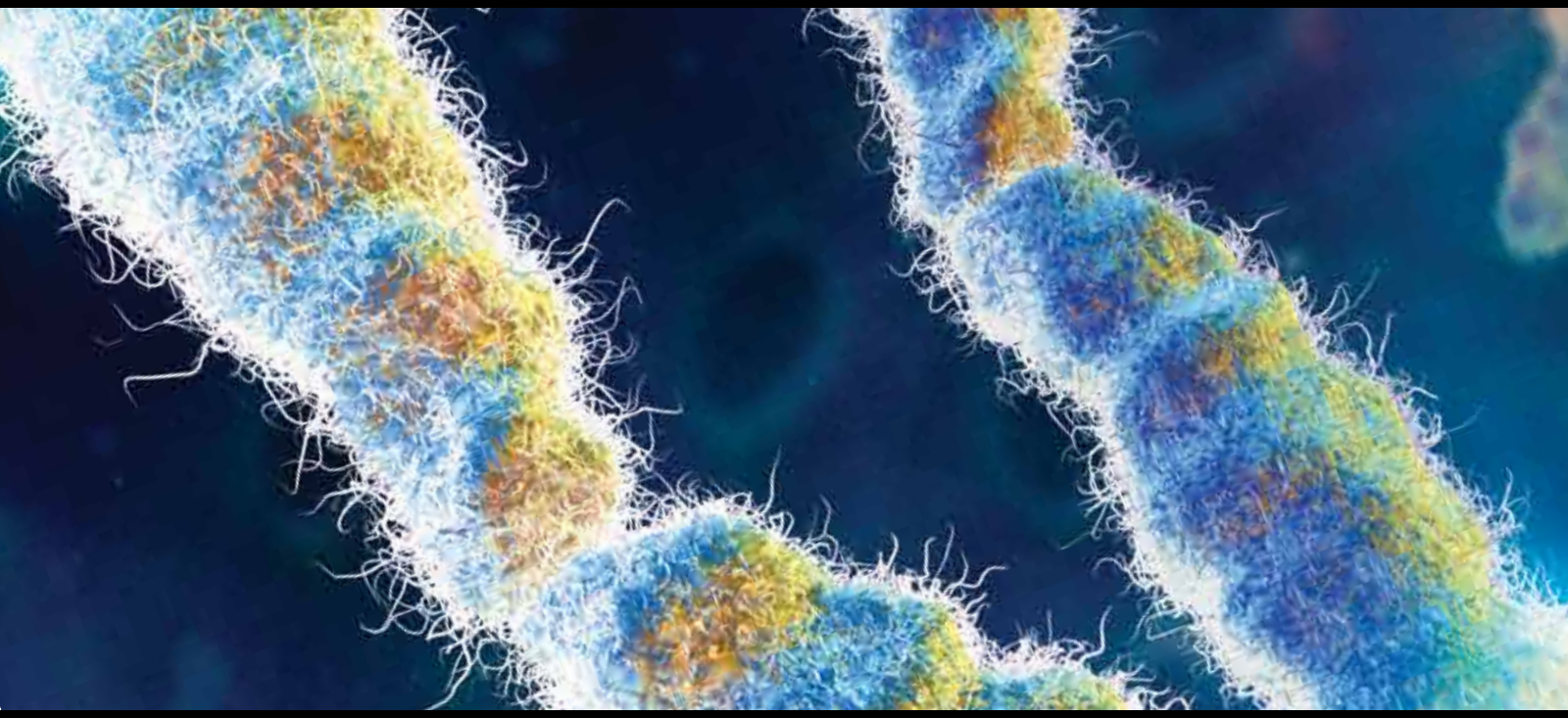
Journal of Aging Research

Aging and Type 2 Diabetes: Consequences for Motor Control, Musculoskeletal Function, and Whole-Body Movement

Guest Editors: Neil D. Reeves, Bijan Najafi, Ryan T. Crews, and Frank L. Bowling



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Editorial Board

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Editorial

Aging and Type 2 Diabetes: Consequences for Motor Control, Musculoskeletal Function, and Whole-Body Movement

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As highlighted by data in 2010 showing that 27% of US residents aged over 65 years have type 2 diabetes compared to 11% of people aged over 20 years, the risk of developing type 2 diabetes increases with advancing age. Accordingly, type 2 diabetes is predicted to rise concurrently with the increasing age of global populations. Diabetes causes a number of complications that negatively impact on the musculoskeletal system and the individual's capacity to perform a number of daily physical activities. It leads to impaired physical capacity through a number of mechanisms such as muscle weakness, limited joint range of motion, and damage to peripheral nerves (neuropathy). Persons affected tend to walk more slowly, with greater variability of gait, and are at increased risk of falling. Lower extremity complications are common, in particular 25% of diabetics develop a foot ulcer at some point. These difficult to heal ulcers commonly lead to amputation secondary to infection.

The vast majority of studies in diabetes patients evaluate gait within a laboratory setting. It may, however, be enlightening to study gait of diabetes patients in their natural environment where conditions may be different from those presented in the laboratory. E. D. de Bruin et al. present data showing the validity and reliability of a portable wearable sensor system for measuring gait parameters in an outdoor setting. They show that walking speed, cadence, step duration, and step length can be measured reliably in a challenging outdoor environment with diabetes patients. They further show that this portable system is able to discriminate between subgroups of diabetes patients with neuropathy based upon their step length.

Diabetic plantar ulcers develop predominantly due to high foot pressures applied during gait along with other risk factors such as neuropathy, vascular insufficiency, and foot deformities. When foot ulcers become infected, amputation may be considered the most appropriate course of action. In their paper, M. Tagoe and R. McCallum present a consecutive case series of their experience with transmetatarsal amputations in diabetic patients. This surgical procedure prevents further proximal spread of infection, whilst maximising limb function and maintaining a substantial portion of the foot. This procedure requires a sound understanding of functional anatomy via splitting and redirecting the tibialis anterior tendon to preserve an effective gait.

Charcot foot is a devastating complication of diabetes with a twofold higher rate of major amputation compared to those without Charcot. The diagnosis can in fact be missed up to 95% of the time. A temperature difference (>2°C) between each foot can be indicative of a Charcot foot excluding other causes, but these measurements are typically taken at rest without considering the effect of plantar stress. B. Najafi et al. investigate a new approach for detecting temperature gradients between feet as a function of the number

of steps walked. In this study B. Najafi et al. used a thermal imaging camera and custom analysis software to determine differences in plantar temperature after walking various distances and between diabetic groups with and without Charcot foot. They found that the thermal response to the graduated walking activity is a sensitive parameter to identify acute Charcot among patients with diabetes and peripheral neuropathy.

People with diabetes are weaker and have smaller muscles compared to matched controls without this condition, which will impact upon their ability to produce the required forces during activities of daily living. However, if the muscle area is infiltrated by noncontractile tissue, the muscle's force producing capability will be even lower than that estimated based upon its gross size. In their paper, L. J. Tuttle et al. measure the intramuscular adipose tissue present in the lower limb muscles of obese participants and diabetes patients with and without neuropathy. They show an increased ratio of intramuscular adipose tissue to muscle volume in the gastrocnemius compared to other lower limb muscles and also find negative correlations between various physical performance measures and calf muscle intramuscular adipose tissue/volume ratio.

Although muscle weakness is present in people with diabetes, skeletal muscle is remarkably adaptable. Resistance training programs are a well-established method for improving form and function, with various clinical and nonclinical populations showing increases in muscle size and strength after a period of training. N. Hovanec et al. perform a systematic review of the literature for the effects of resistance training on metabolic, neuromuscular, and cardiovascular function in older adults with type 2 diabetes. They find that resistance training can have a positive effect, with the largest effect found on the musculoskeletal system, benefits were also reported in aspects of the diabetic disease process, and to a lesser extent on changes in body composition.

In addition to being problems in their own right, complications from diabetes such as neuropathy, muscle weakness, foot and body pain, pharmacological complications, and specialty (offloading) footwear devices all contribute to individuals with diabetes being at higher risk of falling. The annual incidence of falls in the elderly with diabetes has been previously reported to be 39%. Furthermore, these individuals are at higher risk of fracture, have poorer rehabilitation results, and are at a higher risk of recurrent falls than their nondiabetic counterparts. Fortunately balance, strength, and gait training have been shown to successfully reduce fall risk in this population. The above issues relate to a "growing troubling triad" presented by diabetes, aging and falls and are reviewed in a paper by R. T. Crews et al.

Diabetes and its associated complications present a number of challenges for motor control, musculoskeletal function, and whole-body movement. The high-quality collection of papers in this special issue furthers our understanding of these challenges. We hope that this special issue will inform and interest the reader and contribute to scientific understanding in this area.

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Review Article

A Growing Troubling Triad: Diabetes, Aging, and Falls

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There is a significant and troubling link between diabetes (DM) and falls in the elderly. Individuals with DM are prone to fall for reasons such as decreased sensorimotor function, musculoskeletal/neuromuscular deficits, foot and body pain, pharmacological complications, and specialty (offloading) footwear devices. Additionally, there is some concern that DM patients are prone to have more severe problems with falls than non-DM individuals. Fractures, poorer rehabilitation, and increased number of falls are all concerns. Fortunately, efforts to mitigate falls by DM patients show promise. A number of studies have shown that balance, strength, and gait training may be utilized to successfully reduce fall risk in this population. Furthermore, new technologies such as virtual reality proprioceptive training may be able to provide this reduced risk within a safe training environment.

1. Introduction

From 2000 to 2010 the elderly (65+ years) population in the USA has continued its upward trend, increasing by 5.25 million (15%) to a total of 40.26 million [1]. This amounts to 13% of the entire population [1]. Thanks to the aging baby boomers population, by the year 2050 the elderly population is expected to reach 88.5 million, which would represent 20% of the total population [2]. One of the greatest health challenges facing this population is falls. In 2000 there were a reported 10,300 fatal falls by the elderly in the USA that incurred $179 million in direct medical costs [3]. There were an additional 2.6 million medically treated falls that cost $19 billion in medical costs. Other western nations report similar significant burdens with the United Kingdom reporting £981 million (US $1.9 billion) in costs for falls in those 60 or more years old in 1999 [4], and in 2001 the annual cost of care attributable to falls in those 65 or older in Australia was $86.4 million (US $66.1 million) [5]. While the cause of falls is often multifactorial, diabetes mellitus (DM) has been shown to be a significant factor. The significance of the relationship between aging, DM, and falls has been highlighted by previous work that found the annual incidence of falls in elderly individuals with DM to be 39% [6]. This paper will review the association of fall occurrence and diabetes, the association of fall severity and diabetes, and efforts to limit diabetes associated risks for falls.

2. Association between Diabetes and Falls

Falls are a major concern for elderly adults with DM [7]. The high prevalence of falls in ambulatory elderly individuals with DM is well established with reported annual incidence rates of 39% in those over 65 years [6] and 35% in those over 55 years [8]. In addition to the reported high incidence of falls in this population, it has been established that DM individuals are at a higher risk for falls [9, 10]. There are a number of mechanisms by which DM may contribute to falls. Decreased sensorimotor function, musculoskeletal/neuromuscular deficits, foot and body pain, pharmacological complications, and specialty (offloading) footwear devices will be discussed.

3. Decreased Sensorimotor Function

Diabetic peripheral neuropathy (DPN) is common among the DM population, and its prevalence increases with age and duration of diabetes [11–13]. While a number of detrimental changes to the nervous system fall under the umbrella of

DPN, this section will focus on the most common type which is damage to the large nerve fibers that results in decreased sensorimotor function [14]. DPN patients with diminished plantar sensation on their feet have been observed to exhibit increased postural sway along with significant loss of postural control [15, 16]. Loss of proprioceptive feedback [17] during standing and walking in turn leads to increased risk of falls which is evident from a recent prospective cohort study on 9,249 women aged above 67 years where postural instability and DPN were observed to account for the largest percentage of the relationship between diabetes and falls [18]. Cross-sectional studies have also found a strong association between the development of DPN and falls. Among 21 DM patients over 55 years who reported at least one fall in the past year, MacGilchrist et al. found that 86% had peripheral neuropathy [8]. Furthermore, it has been shown that as DPN severity increases, performance on functional reach tests declines [19]. Thus, as DPN severity increases, there is a higher risk of falls occurring while completing reaching tasks in the standing position. While there are many risk factors that contribute to falls, DPN is definitely a significant contributor [20].

4. Musculoskeletal/Neuromuscular

Apart from DPN, lower physical activity, muscle strength, and poor postural control were also found to be among the significant risk factors that influence gait patterns and increased risk of falls among the DM population [21, 22]. Among the elderly population, postural control is an important factor to perform activities such as standing, sitting, walking, and reaching tasks [23–25]. Considering that the feet serve as the base supporting structure during these activities, the strength in lower extremity joints plays a vital role in establishing a strategy for postural stability [26]. Impaired postural control during static balance tests [27] as well as dynamic short whole body anterior translations of 1–4 mm in older patients with DM [28] increases the limitations at the base of support and in turn results in increased risk of falls.

In addition to the lack of sensorimotor function discussed previously, coordination of muscles for postural compensatory strategies is challenged in individuals with DPN. Najafi et al. [17] utilized a novel compensatory index for quantifying postural control strategy to compare strategies utilized by healthy young subjects to strategies of older DPN subjects. In comparison to the healthy young, the older DPN subjects had a significant 10% reduction in postural compensatory strategy. This was coupled with a 98% increase in postural sway. This difficulty in postural control coupled with an altered gait pattern [29] further increases the risk of falls in DPN patients.

Low plantar flexion strength has also been observed to be associated with increased center of mass (COM) displacement or sway among DM patients negatively affecting the maximum forward reach distance [24]. Accordingly, while studying ambulatory DM patients, Macgilchrit et al. found that ankle plantar flexion muscle strength was lower among fallers by 40% compared to nonfallers [8]. Reduced muscle strength has also been shown to result in reduced walking speeds [25, 30], and an increased double support phase of the gait cycle. Studies have shown increased double support time to be a significant factor for falls [31–33] especially in people with postural instability [34]. Individuals at high risk for falls likely adopt this increased double support strategy in order to limit the time during which they must maintain balance on a single limb. This further emphasizes the need for exercise training and developing a stable postural control strategy in DM patients to reduce the risk of falls.

5. Foot and Body Pain/Pharmacological Complications

While the majority of excess fall risk in patients with diabetes can be attributed to DPN sensorimotor decrements and aberrant neuromuscular control, it is important to recognize that other factors associated with diabetes (e.g., foot and body pain and the use of psychotropic medications and polypharmacy) can also contribute to a heightened fall risk profile.

Foot pain is another recognized risk factor for falls among community-dwelling older adults [35, 36]. Patients with diabetes frequently experience symptoms of painful polyneuropathy as the distal nerve fibers in the toes and foot begin to deteriorate. Similarly, patients with chronic disabilities encounter greater levels of chronic, generalized body pain [37, 38] which also places them at increased risk for recurrent falls [21]. This is because diabetic individuals suffering with chronic pain may be less capable of adhering to productive self-management practices like regular exercise [37] and have poorer mental health and physical functioning [38] which places them at increased risk for falls [35].

Diabetic patients that suffer with neuropathic pain are frequently managed with psychotropic and other central nervous system mediated medications. Amitriptyline and duloxetine hydrochloride, for example, are commonly used to treat the painful symptoms of diabetic neuropathy, the latter being one of only two FDA-approved medications for use in diabetic neuropathy. Psychotropic medications are frequently implicated in falls and nearly double an elderly adult's risk for experiencing a fall [39, 40] and having recurrent falls [21, 41]. Older adults suffering with diabetes are also more likely to be taking a greater number of prescription medications [21] and seem to be more sensitive to the effects of polypharmacy than their nondiabetic counterparts [40, 42]. Patients with diabetes start to experience an increased risk of falling with regimens involving just 4 or more prescription medications [42].

One of the hazards of managing diabetes is the increased risk for experiencing unexpectedly low blood glucose levels and symptomatic hypoglycemia. Hypoglycemic episodes can occur with oral hypoglycemic and/or insulin use and frequently result in a state of dizziness, confusion, and postural instability which increases ones' risk for a fall accident [43–46]. While the literature has been somewhat mixed regarding the extent to which the level of diabetes control influences fall

risk [42, 47, 48], it remains clear that the medications associated with treating DM and its complications can contribute to increased fall risk.

6. Offloading Footwear

Footwear such as athletic shoes has been found to reduce fall risk in older adults [49, 50]. Within the DM population, foot ulcers are highly prevalent [51, 52] and often develop due to cumulatively high localized plantar pressure on their feet [53–55]. In order to reduce the risk of ulceration and also for treatment of ulcers, footwear that provides offloading of the localized stress is widely used [55–57]. Even though offloading footwear has not been directly associated with falls, some offloading devices have certainly been found to negatively affect postural stability [58, 59]. Of most concern are the casts and cast walkers used in the treatment of diabetic foot ulcers. These devices significantly restrict normal gait. In addition to being heavy, prohibiting ankle movement, prohibiting normal heel to toe progressive loading of the foot, and potentially decreasing proprioception, some offloading footwear also creates a limb length discrepancy [60]. Given the association of postural stability to fall risk [61], reduced postural stability due to offloading footwear will increase the risk of falls of those utilizing the footwear. Design modification for offloading footwear such as reduction in strut height and reduced weight has been suggested as a means to improve postural stability [62] which might in turn reduce fall risk.

7. Association of Fall Severity and Diabetes

In an editorial concerning complications of diabetes in elderly people, Gregg et al. noted that falls and fractures along with cognitive disorders, physical disability, and other geriatric syndromes may be as great a concern to older people with diabetes as the more traditionally recognized vascular complications [63]. Diabetes increases not only the risk of falls, but also the risk of fractures [64, 65]. Strotmeyer and coworkers found older adults with diabetes to be at higher fracture risk compared with nondiabetic adults with similar bone mineral density [65]. The literature suggests that the fracture risk point estimates described in type 1 diabetes are considerably higher than in type 2 diabetes [66]. However, increased fracture risk in longstanding type 2 diabetes is a paradoxical phenomenon because men and women with type 2 diabetes typically have normal to high bone mineral density [67–69]. Altered body composition and microvascular complications, including retinopathy, peripheral and autonomic neuropathy, hypoglycemia, and use of medications, particularly thiazolidinediones, are all related with increased risk of fractures in older adults with diabetes [7, 70].

In addition to a predisposition to fractures with falls, individuals with DM may be prone to poorer rehabilitation. In investigating rehabilitation following hip fracture, Semel et al. [71] found that patients with diabetes had worse outcomes. The authors noted that patients with diabetes had a worse length of stay efficiency (a measure of recovery per each day of hospital stay) compared with other patients. Similarly, when Liberman et al. compared 224 patients with diabetes to 738 patients without diabetes in a prospective cohort study, they found that patients with diabetes had a worse functional outcome following rehabilitation after hip fracture surgery [72]. Ekstrom and colleagues evaluated the health-related quality of life (HRQoL) after hip fractures and noted that patients with diabetes mellitus had more pain, comorbidities, and reduced health status preoperatively than patients without diabetes. The authors further noted that while there were no more medical complications among patients with diabetes during the first postoperative year, cardiac ($P = 0.023$) and renal failures ($P = 0.032$) were more frequent in patients with diabetes at 24 months.

One last factor to consider in the severity of falls is the occurrence of recurrent falls. Pijpers et al. compared the incidence of recurrent falls in older people with and without diabetes with a mean followup of 139 weeks and noted that 30.6% of the individuals with diabetes and 19.4% of the individuals without diabetes fell recurrently (incidence rate of 129.7 versus 77.4 per 1,000 persons-years, respectively, HR = 1.67 (95% CI: 1.11–2.51)) [21]. The authors noted that the greater number of medication, higher levels of pain, poorer self-perceived health, lower physical activity and grip strength, more limitations in activities of daily living, lower-extremity physical performance, and cognitive impairment may potentially increase the risk of recurrent falls, and these variables together accounted for 47% of the increased risk of recurrent falls associated with diabetes (adjusted HR = 1.30 (0.79–2.11)).

8. Combating DM-Related Fall Risks

A recent publication regarding falls of elderly people in long-term care facilities found that 49% of falls in this setting occurred while walking, 24% while standing, and 21% while either rising up or lowering oneself [73]. In studying daily physical activity patterns of DPN subjects with a mean age of 59 ± 8 years, it was found that each 24 hr day these subjects spend 13.5% of their time standing and 6.1% walking and performed 77 sit-to-stand postural transitions per day on average [74]. Therefore, unfortunately there are plenty of opportunities for elderly adults with DM to experience a fall. Accordingly, numerous investigations regarding improving balance, strength, and gait in order to reduce falls have been conducted [27, 30, 75–77].

Weekly balance training sessions with or without additional strength and/or gait training have been shown to reduce fall risk in DM patients [27, 30, 75, 76]. Positive outcomes have been found both in the broad perspective of DM patients in general [76] as well as specifically in DPN patients [30, 75]. What is more promising is that in a study comparing four groups (DM with fall history $n = 7$, DM without fall history $n = 9$, non-DM with fall history $n = 7$, non-DM without fall history $n = 14$), the greatest improvements were seen in DM patients with a history of falling [27]. One study to actually track fall occurrence following

implementation of a strength and balance program for DPN patients did not show a reduction in falls compared to a DPN control group; however, there were several limitations to the study [77]. This was a secondary analysis of a study utilizing subjects with a somewhat low minimum age criteria of 50. Also the majority of the prescribed intervention was to be conducted at home without supervision. Only 8 training sessions were conducted with a physical therapist, all of which occurred during months 1–3. The first balance and strength assessments to occur after initiation of training did not occur until 6 months after study initiation. Finally no information was provided concerning compliance of exercise at home and only 45% of participants in the intervention group completed "more than half of the required study protocol elements (p. 1572)." In contrast, a study comparing home-based versus "center-based" balance and strength training for 107 community-dwelling adults (DM was not an inclusion criteria) referred for a falls prevention service found that the center-based service demonstrated significantly better results in preventing falls [78].

In addition to traditional balance and strength training, new technologies utilizing virtual reality may provide additional training methods with limited patient risk. It has been previously shown that DM patients either without or with minimum DPN demonstrate reduced toe-obstacle clearance with altered gait patterns during obstacle crossing [79]. In addition to increasing fall risk during daily living, training to improve clearance could be risky in that falls may occur during training sessions requiring subjects to step over obstacles. Recently an investigation validated a virtual reality protocol for assessing obstacle crossing while stepping in place [80]. The study showed that DPN participants had greater difficulty completing the virtual obstacle crossing. It is possible that this paradigm could be used as a minimal risk training program to improve real world obstacle crossing and subsequently reduce fall risk.

9. Conclusion

Falls in elderly individuals with DM are a significant burden to the healthcare system. A number of factors tied to DM predispose this population to a higher risk of falls. Additionally, the falls that this population suffers from have the potential to be more severe in terms of injuries sustained as well as the recovery process. Therefore much work is ongoing regarding the reduction of falls in this population. Numerous studies utilizing balance, strength, and/or gait training have demonstrated reduced fall risk for DM patients that undertook the training. More prospective work is needed regarding the long-term outcome of these interventions on actual fall prevention.

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Review Article

Resistance Training and Older Adults with Type 2 Diabetes Mellitus: Strength of the Evidence

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Objective. This paper analyzes the effects of resistance training (RT) on metabolic, neuromuscular, and cardiovascular functions in older adults (mean age ≥ 65 years) with type 2 diabetes (T2DM). *Research Design and Methods*. A systematic review conducted by two reviewers of the published literature produced 3 records based on 2 randomized controlled trials that assessed the effect of RT on disease process measures and musculoskeletal/body composition measures. Statistical, Comprehensive Meta-Analysis (version 2) software was used to compute Hedge's g, and results were calculated using the random effects model to account for methodological differences amongst studies. *Results*. Largest effect of RT was seen on muscle strength; especially lower body strength, while the point estimate effect on body composition was small and not statistically significant. The cumulative point estimate for the T2DM disease process measures was moderate and statistically significant. *Conclusions*. RT generally had a positive effect on musculoskeletal, body composition, and T2DM disease processes measures, with tentative conclusions based on a low number of completed RCTs. Thus, more research is needed on such programs for older adults (≥65 years) with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) in older adults is an emerging epidemic [1]. (For the purpose of this paper, the term "older adults" refers to individuals who are at least 65 years old.) It is an age-prevalent metabolic disorder, characterized by insulin resistance with relative insulin deficiency [2, 3], with the highest prevalence found in individuals who are 80 years or older—an estimated number of 40 million is expected in the United States by the year 2050 [1].

Physical activity is considered to be a cornerstone of T2DM prevention and management [2, 4], and it is important to have accurate information for health care organizations to integrate into their knowledge management strategies [5]. Physical activity refers to "the expenditure of energy above that of resting by contraction of skeletal muscle to produce bodily movement," while exercise is "a type of physical activity that involves planned, structured and repetitive bodily movement performed for the purpose of improving physical fitness" [6, page 359]. Physical activity and exercise will be used interchangeably in this paper.

In terms of physical activity as a management method in populations living with T2DM, traditional focus has been given to aerobic training (AT) interventions [7, 8]. Aerobic training activates large muscle groups to perform activities such as swimming and running, increasing the function of the heart, lungs, and muscle mitochondria to meet the heightened oxygen demands, ultimately resulting in cardiorespiratory fitness improvements [9]. Over the past decade, interest has also emerged in conducting studies that assess the potential effect of resistance training (RT) interventions in older individuals with T2DM [10–12]. Resistance training activates the muscular system to generate force against a resistive load [4]; it can be performed by utilizing various exercise machines, lifting free-weights (e.g., dumbbells), or doing calisthenics such as situps, pushups, crunches, and lunges. If RT is performed regularly, where the weight lifted is increased to moderate (50% of 1RM

(1RM represents 1 Repetition Maximum, which refers to the maximum weight that a person can lift once)) and high levels of intensity (>75% 1RM), it often leads to increased muscle mass and improvements in muscular fitness [4, 13–15]. Muscular fitness refers both to muscle strength, the amount of force produced by a muscle, and muscle endurance, the ability of a muscle to "exert submaximal force for an extended period of time" [16, page 27].

Resistance training may be more appealing and feasible than AT for people with T2DM who are often overweight and sedentary [17], as well as for older adults, obese, and/or frail individuals [4, 12, 18]. With advanced age, there is a significant loss of muscle mass and strength, a phenomenon known as sarcopenia [19]. It has recently been indicated that older adults with T2DM tend to have greater muscle mass loss, worse muscle quality (defined as the amount of muscle strength per unit of regional muscle mass), reduced upper and lower body strength, greater visceral adipose content, as well as higher risk for functional decline and disability than their healthy, age-matched counterparts [20–24]. Resistance training might benefit older adults living with T2DM through muscle hypertrophy, enhanced muscle quality, strength gains for greater power development with more effective mobility function, and glycemic profile improvements [25].

Resistance training studies in populations with T2DM were not readily available prior to 1997 [4]. The first physical activity guidelines specifically designed for adults with T2DM were developed by the American College of Sports Medicine (ACSM) in the year 2000 [10]. As illustrated in Figure 1, a modified timeline first introduced by Hills and colleagues in 2010 [26], agencies such as the Canadian Diabetes Association (CDA), the American Diabetes Association (ADA), the Canadian Society for Exercise Physiology (CSEP), and ACSM now include RT recommendations within their physical activity guidelines [11, 27–37].

Due to the associated increases in blood pressure (BP) that may be harmful, there could be unsubstantiated apprehension in recommending RT, especially at higher intensities. The main concern is that these BP increases could lead to a stroke, myocardial ischemia, or retinal hemorrhage [4]. This may partially explain the historical dominance of AT interventions in populations living with T2DM. However, there is a lack of scientific evidence that RT actually increases any of the aforementioned risks, as no RT-related adverse events have been reported in studies where individuals with T2DM were assessed [4, 38]. Additionally, past researchers have suggested that RT may actually reduce BP levels [39–41]. Finally, there are precautions that can be employed to avoid potentially harmful side-effects of exercise, such as avoiding physical activity under certain circumstances (detailed by Gordon in 2002 [7]) and conducting appropriate preexercise screens and assessments [7, 35, 42].

Skeletal muscles are the largest postprandial glucose uptake and glycogen storage sites in the human body and as such are integral in maintaining glucose homeostasis. Resistance training may reverse or at least limit some of the aforementioned negative neuromuscular effects associated with aging and/or T2DM [43]. Previous meta-analyses have reported benefits of aerobic training, resistance training, or a combination of the two on reducing HbA1c levels, which signifies improved glycemic control [25, 38, 44–47]. A recent meta-analysis demonstrated that supervised aerobic or resistance training led to greater declines in HbA1c levels than exercise advice only [44]. However, no previous meta-analysis has assessed the effects of RT in older adults (≥65 years) with T2DM. At this time, the literature base may benefit from such a review, since older adults often experience detrimental neuromuscular and sensorimotor changes associated with aging (e.g., sarcopenia) placing them at an increased risk for mobility problems, injury from falls, and disability [21, 48]. Furthermore, T2DM is most common in older adults, who as a result of this disease often experience various comorbidities [49], further reducing their capacity to live independently (e.g., retinopathy, which may lead to blindness; peripheral neuropathy, which may lead to foot ulcers and amputations; nephropathy, which over time could result in renal failure, etc.). Thus, the purpose of this paper is to conduct a systematic review of the best available evidence, in order to assess the effect of RT on metabolic, neuromuscular, and cardiovascular functions in older adults with T2DM.

2. Methods

This meta-analysis utilized the PRISMA as a framework when selecting studies for inclusion in this paper [50]. This meta-analysis is not registered with any institution, such as the Cochrane Collaboration. The literature search was conducted until the end of August 2011, using electronic databases (Medline, EMBASE, AMED, PubMed, Scopus, CINAHL) that generated MESH terms based on the following keywords: resistance training, type 2 diabetes, and aged. The search terms were entered into the databases using the appropriate combinations of "OR" and "AND." In order for articles to be included in this paper, the following inclusion and exclusion criteria needed to be satisfied.

Inclusion Criteria

(i) RCTs.

(ii) Published between the years 2000 and 2011.

(iii) RT interventions or a combination of RT and other forms of intervention (e.g., flexibility, weight loss, standard care, etc.).

(iv) Participants with established T2DM.

(v) Participants' mean age ≥65 years.

Exclusion Criteria

(i) Participants with the presence of another chronic illness (e.g., cancer).

(ii) Non-English publications.

(iii) Studies reporting effect of RT in previously trained participants.

Table 1: Outcome measures.

Body composition measures	Musculoskeletal measures	Type 2 diabetes process measures
		Fasting glucose (mmol/L)
	Muscle strength	
	(i) Upper body strength	Glycosylated hemoglobin (HbA1c) (%)
	(ii) Lower body strength	
Whole body lean tissue mass (kg)	Muscle quality (defined as 1RM strength kg/unit lean body mass kg)	Blood pressure
		Serum/fasting insulin (pmol/L)
Whole body fat mass (kg)		
	Muscle fiber size	Lipids
	(i) Type I cross sectional area (CSA) (μm^2)	(i) Total cholesterol (mmol/L)
	(ii) Type II CSA (μm^2)	(ii) HDL cholesterol (mmol)
		(iii) Triglycerides
		(iv) Free fatty acids (FFAs) (μmol/L)

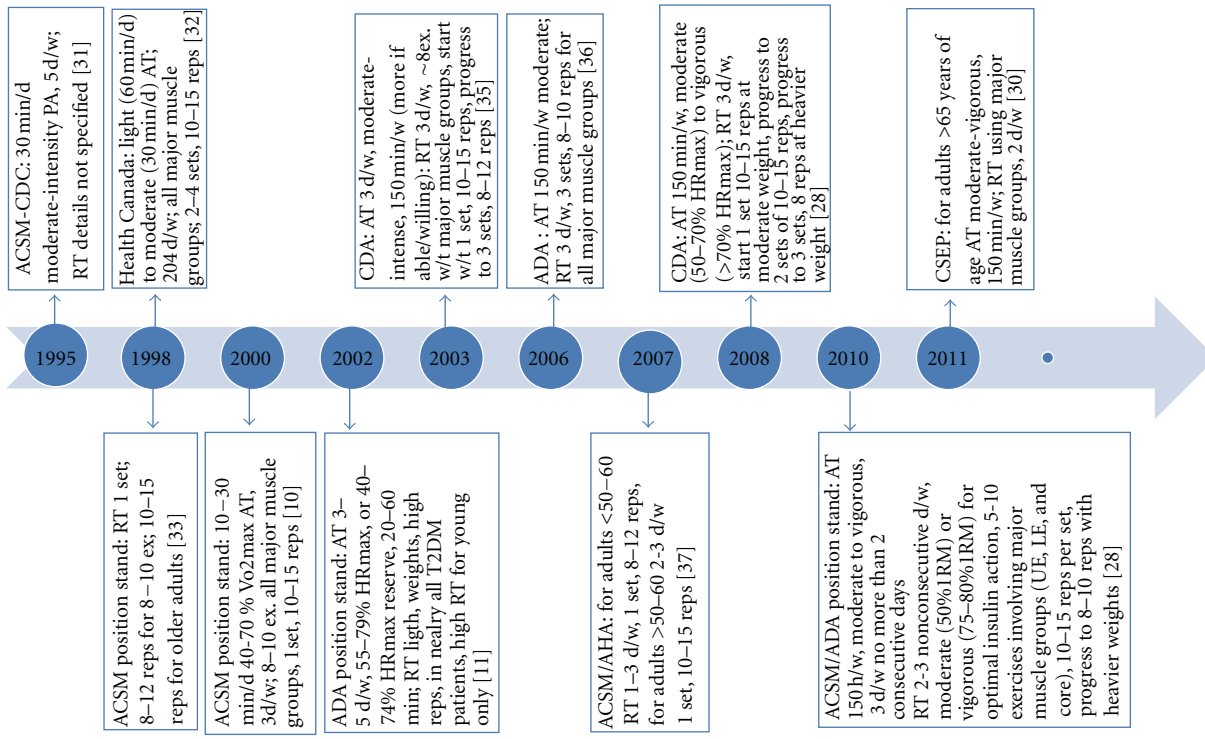

Figure 1: Chronological Timeline of PA Recommendations for T2DM from Various Professional Organizations [modified from [26]]. PHAC [Public Health Agency of Canada]; CSEP [Canadian Society for Exercise Physiology]; CDA [Canadian Diabetes Association]; ACSM [American College of Sports Medicine]; ADA [American Diabetes Association]; CDC [Centers for Disease Control and Prevention]; AHA [American Heart Association]. PA [Physical Activity]; RT [resistance training]; AT [aerobic training]; UE [upper extremity]; LE [lower extremity]; HR_{max} [maximum heart rate]; $VO_{2\,max}$ [maximal oxygen uptake/consumption]; d [days]; w [week]; w/t [with]; reps [repetitions]; ex [exercises]; h [hour]; min. [minute].

(iv) Studies reporting effect of RT on outcome measures not relevant to this paper (see Table 1 for all relevant outcome measures).

The aforementioned inclusion and exclusion criteria were developed in order to obtain the most recent (2000–2011), scientifically rigorous (RCTs) evidence on the specific effect of resistance training in older adults with type 2 diabetes. Various studies, review articles, and commentaries that did not satisfy the inclusion criteria were used to inform the introduction and the discussion sections of this paper. Furthermore, NH and AS independently reviewed and rated the articles and any differences were resolved by discussion or by comparison to the ratings provided on the PEDro website. To limit redundancy, Cohen's Kappa values were not calculated since there were no major disagreements between the authors (i.e., >95% agreement).

Outcome Measures. The primary outcome measures were grouped into three major areas including body composition, musculoskeletal, and type 2 diabetes disease process measures. Table 1 summarizes the major outcome headings and their respective measures.

Methodological Quality of the Studies. Internal validity of studies included in this paper was assessed using the PEDro

Table 2: Participant characteristics.

Source	Group (n)	Age (years)	Gender (M/F)	Whole body fat mass (kg)	BMI (kg/m^2)	Diabetes duration (years)	HbA1c (%)	Fasting glucose (mmol/L)	Fasting insulin (pmol/L)
*Brooks et al. [17]	Exercise 31	66 ± 11.1	10/21	35 ± 5.6	30.9 ± 6.1	8 ± 5.6	8.7 ± 5.6	8.79 ± 2.7	116 ± 167.4
Castaneda et al. [13]	Control 31	66 ± 5.6	19/12	33.7 ± 13.4	31.2 ± 5.6	11 ± 5.6	8.4 ± 1.7	9.85 ± 3.8	115 ± 176.9
Dunstan et al. [53]	Exercise 16	67.6 ± 5.2	10/6	33.1 ± 7.4	31.5 ± 3.7	7.6 ± 5.4	8.1 ± 1	9.5 ± 2.3	132.9 ± 63
	Control 13	66.5 ± 5.3	6/7	35.6 ± 6.8	32.5 ± 3.8	8.8 ± 7.9	7.5 ± 1.1	9.4 ± 2.1	101.9 ± 25.8

All measures are provided as means ± SD.
*Brooks et al. [17] and Castaneda et al. [13] included the same cohort of participants.

scale—a valid [51] and reliable [52] tool to evaluate study quality. Article ratings are included as PEDro scores listed in Table 3, while rating criteria are detailed in Table 5.

Statistical Analyses. Statistical software (Comprehensive Meta-Analysis—version 2) for meta-analysis of binary, continuous, and diagnostic data was used for computation of Hedge's g (a measure of effect size). Hedge's g values were used to assess the influence of strengthening exercises on body composition, musculoskeletal measures, and type 2 diabetes disease outcomes (previously summarized in Table 1). The effect sizes were interpreted as small, medium and large if they were 0.2, 0.5, and 0.8, respectively [54]. A 95% confidence interval was constructed around the point estimate of the effect size. Any standard errors that were reported by study authors were converted to standard deviations using the formula SD = $\sqrt{n} * \text{SE}$, where SD is the standard deviation, $\sqrt{}$ is the square root symbol, n refers to the sample size, $*$ represents the multiplication function, and SE is the standard error [55].

The statistical significance of the differences in the effects of RT on body composition, muscle quality, and strength along with moderator variables included for the effect on disease processes was computed by Page's L statistic with the use of PASW 18 statistical software to calculate the sum of squares (SS) between groups, as well as total SS. Page's L statistic was then calculated using the formula $L = [N - 1]r^2$, where N is the total number of effect sizes and r^2 is the product of $\text{SS}_{\text{between}}/\text{SS}_{\text{total}}$. (Further details regarding Page's L statistic can be found in [56]) When performing meta-analysis, the overall effect of an intervention can be influenced by use of particular outcome measures or intervention strategies. Page's L statistics was utilized to elucidate such differences in the current study.

The presence of heterogeneity among the moderator variables was evaluated by the Q statistic using a random effects model. The studies were considered heterogeneous if the P value of the Q statistic was <0.1, which has been proposed as the appropriate alternative to the conventional $P < 0.05$, when there is a low number of articles included in a review [57]. Publication bias was not assessed, since there were only three articles included, and any conclusions that are drawn from the results that emerge from this meta-analysis cannot be taken as definitive. The robustness of the findings was established based on the assessment of the effect size and its associated confidence intervals, rather than other methods, such as the calculation of Fail Safe N, which can lead to widely varied estimates [58]. The results reported were calculated using the random effects model, in order to account for methodological differences amongst studies. The statistical significance for the effect sizes' statistical tests (i.e., Hedge's g) was set at $P < 0.05$.

3. Results

Three [13, 17, 53] of the 446 citations were included in the final analysis (Figure 2). However, 2 of the citations [13, 17] are technically considered one study, since their findings are based on the same pool of participants, but they are both included in the meta-analysis since each of them provides relevant but different outcome measures. A total of 32 effect sizes, evaluating the effect of strength training on the disease process (20 effect sizes) and muscle quality (12 effect sizes), were extracted from the included studies. Participant and study characteristics are described in Tables 2 and 3 respectively.

3.1. Effect of RT on T2DM Disease Process Measures. Serum insulin [17, 53], HbA1c [17, 53], HDL [13, 53], LDL and total cholesterol [13, 53], fasting glucose [17, 53], and BP [13, 53] were analysed to evaluate the effect of RT on the disease process. The overall cumulative point estimate of this effect size was statistically significant (Hedge's $g = -0.246$; $P = 0.023$; 95% CI: −0.458, −0.034).

For individual variables, the effect of RT on BP (Hedge's $g = -0.540$; $P < 0.001$; CI: −0.832, −0.248), insulin (Hedge's $g = 0.505$; $P = 0.016$; CI: 0.094, 0.916), total cholesterol, and LDL cholesterol (Hedge's $g = 22120.464$, $P = 0.002$; CI: −0.760, −0.169) was statistically significant. However, the effect of RT on fasting glucose (Hedge's $g = -0.121$; $P = 0.559$; CI: −0.526, 0.284), HbA1c (Hedge's $g = -0.463$; $P = 0.145$; CI: −1.084, 0.159), and HDL cholesterol (Hedge's $g = 0.134$; $P = 0.517$; CI: −0.271, 0.539) was not as consistent between studies in terms of magnitude of improvement and fluctuations in control group. Also, the differences in effects of RT on fasting glucose, insulin, HBA1c, cholesterol, HDL, FFA, and BP were not statistically significant ($L(19) = 14.109$; $P > 0.05$).

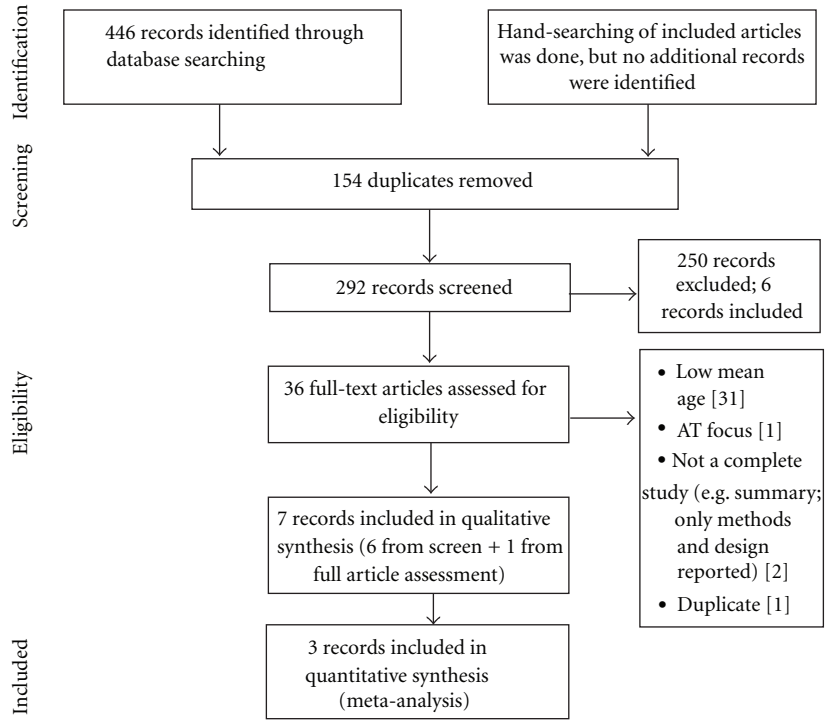

Figure 2: Study selection diagram [50] AT-aerobic training.

3.2. Effect of RT on Body Composition Measures. Lean body mass [17, 53] and fat body mass [53, 59] were analysed to evaluate the effect of RT on body composition. The cumulative point estimate effect of RT on body composition was small but not statistically significant (Hedge's $g = 0.199$; $P = 0.197$; CI: −0.103, 0.500). The effect of RT on lean body mass (Hedge's $g = 0.395$; $P = 0.220$; CI: −0.237, 1.028) was larger than on fat body mass (Hedge's $g = 0.066$; $P = 0.749$; CI: −0.339, 0.471), but neither was statistically significant.

3.3. Effect of RT on Musculoskeletal Measures. Whole body, lower and upper body muscles strength [13, 53], and muscle quality were analysed to evaluate the effect of RT on overall muscle strength and quality. The cumulative point estimate effect of RT on muscle strength (Hedge's $g = 1.05$; $P < 0.001$; 95% CI: 0.699, 1.404) and overall quality (Hedge's g = 0.816 $P = 0.008$; 95% CI: 0.216, 1.415) were large and statistically significant. The largest effect of RT was on lower body strength (Hedge's $g = 1.415$; $P < 0.001$; CI: 0.864, 1.967), followed by upper body strength (Hedge's $g = 0.974$; $P < 0.001$; CI: 0.453, 1.494), and both were statistically significant. The effect of RT on whole body strength was also large and statistically significant (Hedge's $g = 0.802$; $P = 0.002$; CI: 0.291, 1.313).

The effect of RT on muscle quality (Hedge's $g = 1.460$; $P < 0.001$; CI: 0.906, 2.015) was large and statistically significant. The differences in effect of RT on body composition, muscle quality, and strength were not statistically significant ($L(11) = 13.762$; $P > 0.05$). However, the CI ranges were wide for all measures (musculoskeletal, disease process, and body composition); as such any conclusion drawn based on the effect sizes and statistical significance needs to be considered with caution.

The heterogeneity (Q-values with their respective df and P values) for all moderator variables is summarized in Table 4. However, the number of studies included in the analysis is too small to infer definitive conclusions regarding heterogeneity.

4. Discussion

The purpose of this paper was to conduct a systematic review and meta-analysis of the currently available evidence, in order to assess the effect of resistance training in older adults with T2DM. The findings generally show that RT has an effect on the musculoskeletal system, disease process, and body composition to varying degrees (see Table 6 for a summary of the outcome measures, their respective effect sizes, and statistical significances). Overall, RT had the largest effect on the musculoskeletal measures, followed by disease process measures, while the smallest effect was seen on the body composition measures.

It is not surprising that RT had the largest effect on musculoskeletal measures, as it is a well-established mode of exercise to induce neuromuscular changes, such as increased muscle size and strength [15]. Specifically, findings from this analysis indicate that RT increases muscle strength and quality. These effects could be quite consequential for the investigated population, as aging and T2DM are linked with reduced muscle mass and strength, increased adiposity, and a sedentary lifestyle [12].

Although the underlying molecular causes of T2DM are unknown, it has been associated with obesity, visceral

Table 3: Study characteristics.

Study ID (reference number), PEDro score	Sample Size (n), intervention design	Intervention (duration, frequency, intensity, session duration, sets of reps, equipment: exercises)	Outcome measure (¥ P value)	Authors conclusion
*Brooks et al. [17] PEDro: 7	Exercise: $n = 31$ RT + SC Control: $n = 31$ SC	(i)16 weeks (ii) 3 d/week (iii) weeks 1–8: 60–80% of baseline 1RM; weeks 10–14: 70–80% of mid-study 1RM (iv) 45 min/session (5 min warmup; 5 min cooldown) (v) 3 sets of 8 reps (vi) 5 pneumatic machines: upper back, chest press, leg press, knee extension, and flexion	Whole-body lean tissue mass (0.04) Lower body muscle strength (<0.001) Upper body muscle strength (<0.001) Muscle quality (<0.001) Type I fiber CSA (0.04) Type II fiber CSA (0.04) HbA1c (<0.001) Fasting insulin (0.27) Fasting glucose (0.92) Whole body strength (0.0001)	16 weeks of RT resulted in musculoskeletal and metabolic improvements, and it is a mode of exercise worth considering as an adjunct to SC
*Castaneda et al. [13] PEDro: 6	Exercise: $n = 31$ RT + SC Control: $n = 31$ SC	(i) 16 weeks (ii) 3 d/week (iii) weeks 1–8: 60–80% of baseline 1RM; weeks 10–14: 70–80% of mid-study 1RM (iv) 45 min/session (5 min warmup; 5 min cooldown) (v) 3 sets of 8 reps (vi) 5 pneumatic machines: upper back, chest press, leg press, knee extension, and flexion	Whole body fat mass (0.26) Total cholesterol (0.59) LDL cholesterol (0.13) HDL cholesterol (0.46) Systolic BP (0.05) Diastolic BP (0.52)	RT was feasible among older adults with type 2 diabetes, and it resulted in improved metabolic control
Dunstan et al. [53] PEDro: 4	Exercise: $n = 16$ RT + WL Control: $n = 13$ WL	(i) 24 weeks (ii)3 d/week (iii) weeks 1-2: 50–60% 1RM; progress to: 75–85% 1RM (iv) 45 min/session (5 min warmup; 5 min cooldown) (v) 3 sets of 8–10 reps (minus abdominal curls) (vi) Free weights and multiple station weight machine; 9 exercises: bench press, leg extension, upright row, lateral pull down, standing leg curl with ankle weights, dumbbell seated shoulder press, dumbbell seated biceps curl, dumbbell biceps kickback, abdominal curls	Total cholesterol (N/A) LDL cholesterol (N/A) HDL cholesterol (N/A) HbA1c (<0.01) Fasting insulin (N/A) Fasting glucose (0.06) Systolic BP (<0.05) Diastolic BP (<0.05)	A 16-week progressive, high-intensity RT program was effective in improving glycemic control and muscle strength in older adults with T2DM

RT: resistance training; SC: standard care; d: days; min: minutes; sec: seconds; b/w: between; reps: repetitions; UE: upper extremity; LE: lower extremity; CSA: cross sectional area; HbA1c: glycosylated hemoglobin; WL: weight loss).
*Brooks et al. [17] and Castaneda et al. [13] include the same intervention and participants but different outcome measures.
¥ P value reported by the authors.

adiposity, and physical inactivity, which all contribute to an increased risk of developing cardiovascular disease and various disabilities [2, 23, 24]. As such, older adults with T2DM are placed at "double jeopardy" with regards to their health status, which greatly increases their dependence on health care services [1]. A large US-based, cross-sectional study illustrated this point when older adults (70–79 years) with and without T2DM were compared [1]. Various publications from this study showed that those with T2DM had lower muscle strength and quality [21], accelerated muscle loss (i.e., loss of knee extensor strength at a more rapid rate), and excessive muscle mass loss (i.e., greater loss in the amount of leg lean mass) when compared with healthy, age-matched counterparts [20, 22]. Reductions in muscle strength and quality have been linked to an increased risk of physical disability, such as mobility problems and falls [48]. Findings from the current meta-analysis suggest that muscle strength and quality improvements in older adults with T2DM could induce greater functional capacity and reduce the risk of disabilities. Furthermore, muscle quality and strength gains may result in greater physical activity participation in various populations [60–62], including older adults with T2DM [13], which could in turn improve this populations' overall health status by reducing negative disease outcomes.

In addition to improvements in muscle quality (the measure of strength per unit of muscle mass), one study

Table 4: Heterogeneity for moderator variables.

Variable	Q-value	df (Q)	P-value
All disease process measures	42.387	19	0.002
BP	2.171	3	0.538
Fasting glucose	0.364	1	0.546
Fasting insulin	0.181	2	0.913
HbA1c	3.099	2	0.212
HDL	0.055	1	0.814
Total cholesterol and LDL	3.079	3	0.380
All musculoskeletal measures	31.313	11	0.001
Muscle quality	8.184	4	0.085
Muscle strength	2.675	2	0.262
Body composition	3.256	3	0.354

that was included in this meta-analysis reported outcomes specifically regarding the cross-sectional area (CSA) of muscle fibers [17]. Although these outcome values could not be meta-analyzed since only one study included these measures, the fact that fiber hypertrophy resulted warrants further discussion. Brooks and colleagues showed that following a 16-week RT intervention the training group increased the CSA of type I and type II fibers, while the control group participants showed the opposite trend—a reduction in the CSA of both fiber types [17]. As well as strength gains leading to more effective force production, the increase in the CSA of muscle fibers, especially type I muscle fibers, might lead to a better delivery of oxygen through the greater capillary density and number of oxidative mitochondria [16]. In addition, these changes may improve the delivery of glucose from the blood to the muscle, while fiber hypertrophy may provide greater glycogen storage capacity within the muscles of individuals affected by T2DM and thus potentially improve insulin resistance [16, 17]. The hypothesis that muscle hypertrophy or larger muscle mass is associated with improved insulin sensitivity and glucose tolerance has previously been recognized [63].

A further elaboration may help to explain how RT might influence the interaction between the neuromuscular system and the underlying disease process of T2DM. Skeletal muscles represent the largest glucose deposition sites in the human body, which is negatively affected by insulin resistance—a defining feature of T2DM [64]. It has been suggested that people with T2DM have a defective insulin-dependent pathway, which is responsible for activating glucose transporters of the muscles to help move the glucose from the blood into the cells [65]. However, individuals with T2DM do not appear to have a flawed contraction-stimulated pathway for glucose transport [65]. For example, RT would induce a muscular contraction, in turn stimulating the translocation of the GLUT-4 (glucose transporter) to the tissue's cell membrane to dock and activate in order to accept the glucose molecules from the blood into the cell. Thus, glucose could enter the cell via this contraction-stimulated pathway even in individuals with T2DM whose insulin-dependent pathway is defective [65]. Furthermore, exercise has shown to increase GLUT4 expression in human skeletal muscle approximately two to four times, leading to improvements in glucose intolerance and insulin action [65–67]. This underlying mechanism may partially explain some of the effects of RT on the disease process outcomes in this meta-analysis.

Resistance training also had some effects on various markers of the disease process associated with T2DM, including HbA1c, BP, fasting insulin, fasting glucose, HDL, total and LDL cholesterol. For example, findings from this meta-analysis indicated a nonsignificant, medium-sized effect of RT on reducing HbA1c, with a wide CI range. This could be the result of low sample size and a few studies; all of the results of this meta-analysis should be considered with caution. Nevertheless, reduction of HbA1c is considered one of the most important markers for glucose control, and a small change or improvement in this marker may result in a significantly reduced risk of developing diabetic comorbidities. Findings from a prospective study might help illustrate this point further, as decreasing HbA1c by 1% could reduce the risk of any diabetes-related complication by 21% [68]. Although this paper cannot confidently conclude that RT can effectively reduce HbA1c levels in older adults with T2DM, a previous meta-analysis by Boulé and colleagues was able to illustrate that RT was equally effective as AT at improving glycemic control in middle-aged adults [25]. On the other hand, recently Jorge and colleagues compared RT, AT, combined AT and RT, and a control group that received standard care [39]. They did not find significant reductions in HbA1c within any of the exercise groups when compared with the control group [39]. However, all groups had small sample sizes and the control group might have improved their diet during the time of the intervention while their standard care medication also could have contributed to the small difference between groups. Previous researchers have demonstrated that, in addition to RT effectively reducing HbA1c levels, it can also increase glucose disposal and storage capacity, improve lipid, as well as cardiovascular disease risk profiles in adults with T2DM [69–71].

This meta-analysis also showed a moderate effect of RT on BP, and a small effect on total and LDL cholesterol. However, the effect of RT on body composition measures, including lean body mass and fat mass, was small and non-significant. The positive effect of RT on BP and cholesterol may be promising, since achieving lower BP with exercise is indicative of improved cardiovascular function, while a reduction in cholesterol levels, especially LDL, may help reduce the risk of micro- and macrovascular complications, such as atherosclerosis, stroke, and myocardial infarction [2]. Past researchers have also found positive changes of BP that might have been induced by RT [39, 40]. These findings may be of considerable value for those with T2DM who have a two- to fourfold greater risk of developing cardiovascular disease [72]; improvements in LDL cholesterol as well as BP could improve health outcomes for this group. Improved physical function could lead to a greater ability to participate in various physical activities safely and enjoyably and in turn reduce the sedentary behavior often found in individuals with T2DM. However, some researchers did not find that RT led to a reduction in BP [53], nor improvements in

Table 5: PEDro rating details.

Study ID (PEDro score)	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate followup	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability
Brooks et al. (7) [17]	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Castaneda et al. (6) [13]	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Dunstan et al. (4) [53]	Yes	No	Yes	No	No	No	No	No	Yes	Yes

Table 6: Summary of resistance training effect on outcome measures.

Outcome		Hedge's g	P value	Effect description (statistical significance)
Disease processes		−0.271¥	0.008	Medium (significant)
BP (systolic/diastolic mmHg)		− 0.540	<0.001	Large (significant)
HbA1c (%)		−0.463	0.145	Medium (not significant)
Total and LDL cholesterol		−0.464	0.002	medium (significant)
Fasting glucose		−0.121	0.559	Small (not significant)
Fasting insulin		0.505	0.016	Medium (significant)
HDL cholesterol		0.134	0.517	Small (not significant)
Body composition		0.199	0.197	Small (not significant)
Lean body mass		0.395	0.220	Small (not significant)
Fat body mass		0.066	0.749	Small (not significant)
Muscle strength		1.05	<0.001	Large (significant)
Lower body muscle strength		1.415	<0.001	Large (significant)
Upper body muscle strength		0.974	<0.001	Large (significant)
Whole body muscle strength		0.802	0.002	Large (significant)
*Further muscle measures		Exercise	Control	P value
Quality	Baseline	61 ± 27.8	51 ± 22.3	<0.001
	Final	100 ± 33.4	48 ± 22.3	
Type I CSA (μm^2)	Baseline	4068 ± 1425.3	4546 ± 1503.3	0.04
	Final	4928 ± 2071.2	4381 ± 1692.6	
Type II CSA (μm^2)	Baseline	3885 ± 1547.8	4330 ± 1926.4	0.04
	Final	4605 ± 1575.7	4201 ± 1870.8	

BP-blood pressure; HbA1c: glycosylated hemoglobin; LDL: low density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; CSA: cross sectional area.

¥ Negative values denote a decrease in the outcome measure (i.e., this is a positive effect, since a reduction in disease processes, such as lowered BP, LDL, and HBA1c, indicates an improvement in disease management).

*Further muscle measures were not entered into CMA; all values are means ± SE, taken from [17].

the LDL cholesterol levels following AT, RT, or combined training [25]. Further studies are needed in order to better understand the potential effect of RT on BP and cholesterol in people with T2DM [53].

The fact that body composition was not altered may be due to the short intervention durations, or it could be attributed to the low number of studies included in this meta-analysis. However, despite RT apparently not having an effect on the body composition of older adults with T2DM, their metabolic control could still be impacted by exercise alone, since Boulé et al. indicated that RT and/or AT can enhance insulin sensitivity and glycemic control even when the weight and/or body composition is unaltered [25]. Future studies are needed to confirm this claim for older adults with T2DM.

Although previous reviews indicate that RT can positively impact functional and metabolic changes in people with T2DM, this is the first meta-analysis that suggests that RT may benefit older adults (≥65 years) in the management of their disease. It is important to have accurate information for health care organizations to be able to integrate physical activity recommendations into their knowledge management strategies [5]. However, there are insufficient high quality studies (only 2 original RCTs, providing 3 records) that

address the full impact of RT in older populations with T2DM. As such, confidence in conclusions based on the presented findings is limited. Furthermore, no study has included RT interventions with adults who were 80 years or older, despite this age group having the highest prevalence of T2DM [1]. Given the high prevalence and incidence of T2DM in geriatric populations [73], more research is needed to assess the potential benefits of RT for this age cohort. Also, some studies have suggested that there is an additive benefit from combining AT and RT exercises for adults with T2DM [9, 74, 75]. Future research should explore the effect of combined exercise training in populations who are at least 65 years old.

Finally, the importance of conducting appropriate preexercise screens prior to implementing an RT or any exercise intervention cannot be overlooked [7]. This is of particular interest when working with older/clinical populations who may have various complications and comorbidities, resulting in absolute or relative contraindications to physical activity detailed in [7, page 276] and elaborated further by other researchers [18, 49].

Measures that could provide additional insight into the benefits/risks of RT, such as muscle quality, fiber CSAs, changes in free fatty acid [17], and/or triglyceride concentrations [53], and medication reduction [13] were reported only in some papers and thus could not be meta-analyzed. As a result, a better understanding of the impact of RT in older adults with T2DM requires additional study.

5. Limitations

There are several limitations in this meta-analysis that are worth noting. Firstly, 68% of total participants from all three records are Hispanic. As such, the generalizability of the findings to different ethnic origins may be limited, due to the diversity of psychosocial and potentially genetic factors.

Secondly, using the terms physical activity and exercise interchangeably may have varying outcome implications. For instance, studies that focus on physical activity may report different outcomes and result in alternate findings when compared to studies using a targeted training approach with predefined aims.

Thirdly, the inclusion and exclusion criteria were developed to obtain the most relevant evidence for the population of older adults with type 2 diabetes, but with this strict criteria there is a risk that perhaps relevant studies that did not meet the specified inclusion requirements could have provided some additional insight for this paper.

Fourthly, there is a risk of having a confounding variable effect by including Dunstan et al. [53], since their RT intervention was combined with a weight loss component. Thus, it is not possible to have a definitive conclusion about the independent effect the RT intervention might have had if it was not combined with the weight loss component.

Despite these limitations, a rigorous approach has been undertaken to provide the first precise meta-analysis that assessed the currently available RCTs for RT effects on metabolic, musculoskeletal, and cardiovascular factors in adults 65 years or older with type 2 diabetes.

6. Conclusion

Although strong conclusions cannot be drawn from this meta-analysis, the potential role of RT to help older adults in the management of T2DM should be considered given the current trends in aging, obesity, and diabetes. In 2005, managing diabetes and its complications cost the Canadian acute healthcare system $5.6 billion [76], while in the US the current approximated annual cost is surpassing $134 billion dollars [1]. Also, these figures are excluding the personal costs endured by those with the disease and their families, associated with morbidity induced by various diabetic complications [1]. More recent statistics suggest that, factoring the cost of undiagnosed diabetes, prediabetes, and gestational diabetes, the total cost of diabetes in the US in 2007 totaled to $218 billion [77]. Considering that 26.9% of older adults in the US (approximately 10.9 million individuals) have diabetes [77], there ought to be specific and appropriately designed interventions for this cohort. Inclusion of RT in the management of T2DM has been recognized and supported by previous reviews [4, 12, 25, 47, 78, 79] and physical activity guidelines [27, 29, 34]. Future studies will help to confirm whether the metabolic benefits obtained with RT in younger populations could also positively impact older adults with T2DM, including the rapidly expanding population aged 80 years or more.

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Research Article

Validity and Reliability of Accelerometer-Based Gait Assessment in Patients with Diabetes on Challenging Surfaces

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Walking on irregular terrain influences gait of diabetic patients. We investigate the test-retest reliability and construct validity of gait measured with the DynaPort MiniMod under single and dual task conditions in diabetic patients walking on irregular terrain to identify the measurement error (precision) and minimal clinical detectable change. 29 patients with Type 2 diabetes were measured once, and 25 repeated the measurement within 7 days. Patients walked on a therapy garden walkway. Differences between three groups of diabetics with various levels of lower extremity neuropathy were analyzed with planned contrasts. ICC was excellent for intervisit measurements with ICC's > 0.824. Bland and Altman Plots, SEM, and SDD showed precise values, distributed around zero for both test conditions. A significant effect of grouping on step length performance hints at possible construct validity of the device. Good reliability of DynaPort MiniMod measurements on a therapy garden walkway and an indication for discriminatory capability suggests that DynaPort MiniMod could facilitate the study of gait in diabetic patients in conditions close to real-life situations. Good reliability, small measurement error, and values of minimal clinical detectable change recommend the further utilization of DynaPort MiniMod for the evaluation of gait parameters in diabetic patients.

1. Introduction

The World Health Organization has described type 2 diabetes as an international epidemic. Current estimates suggest that the number of persons with diabetes will reach 300 million by 2025 [1]. Fifty percent of patients who have diabetes for more than 20 years develop peripheral neuropathy (PN), which affects nerve function from the periphery to more proximal regions [2, 3]. Because the increasing prevalence of diabetes is accompanied by gait problems and a heightened risk of falling, there is an increased need for understanding the possible gait pattern changes diabetic patients are confronted with [4]. It has, furthermore, been demonstrated that patients with diabetes may also improve their gait due to specific exercise programs [5, 6].

In this context gait analysis is usually performed in specialized kinesiology laboratories. Cameras, force platforms, and magnetic and ultrasound systems are thereby often used technologies for the gait analysis [7, 8]. However, time expenditure and financial constraints limit their use in clinical practice [9]. Moreover, gait analyses are traditionally performed indoors, on a predefined, clean, and flat specific pathway. Such conditions enable precise recording but are not representative of the real-life context. Activities of daily life require us to move about in challenging environments and to walk on varied surfaces. Irregular terrain has been shown to influence gait parameters such as speed, especially in a population at risk for falling [10], for example, patients with Diabetes [11, 12]. Furthermore, the fact that falling mainly occurs in a complex environment [13] under

attention demanding conditions emphasizes the need for clinicians to objectively record gait data in a real-life context [14] under dual task conditions [15].

The recent use of body-fixed sensors suggests that they could serve as a tool for analyzing the gait of patients in more challenging walking environments [16–18]. In comparison with other motion measurement devices, body-fixed sensors have the advantage of being lightweight and portable, which enables subjects to move relatively freely. They permit data collection in a challenging environment; they are easy to use, provide a good ratio in terms of cost and amount of information retrieved, and can capture data from many gait cycles. Thus they seem ideal for extending our understanding of gait changes in specific populations by performing measures in real-life conditions, for example, in diabetic patients [19]. An objective evaluation in real-life conditions might help understand the causes of diabetic gait problems and ultimately facilitate the choice or the development of appropriate physical treatment. Therefore, the potential of body-fixed sensor approaches should be investigated in the diabetic population in order to ensure the validity and the reliability of data recorded during gait analysis under single and dual task conditions on changing types of surfaces.

To be clinically useful, an assessment procedure must have a small measurement error to detect a real change and must be able to distinguish between subpopulations for example, diabetic patients with and without various stages of peripheral neuropathy. A test-retest difference in a patient with a value smaller than the standard error of the measurement (SEM) is likely to be the result of "measurement noise" and is unlikely to be detected reliably in practice; a difference greater than the smallest real difference is highly likely (with 95% confidence) to be a real difference [20]. Another example of these statistics is the smallest detectable difference (SDD) [21]. The DynaPort MiniMod body-fixed sensor has previously been shown to be reliable, valid, and valuable in elderly for the analysis of gait performed on challenging surfaces [22–25]. To date, little is known about the variability in gait measures within the diabetic population and the reliable use of accelerometers in these patients. With this in mind, we conducted this study to (a) investigate the validity and reliability of gait parameters measured with DynaPort MiniMod in diabetic patients walking under single and dual task conditions on a challenging walking course, (b) identify the measurement error (precision), and (c) identify the smallest clinical detectable difference. We hypothesized [1] that walking quality in patients with diabetes can be reliably measured with accelerometers [2], that the walking quality is different in patient subgroups (we expect diabetic neuropathy to change gait quality compared to the group with no neuropathy), and [3] we believe that severe neuropathy effects walking quality more than mild neuropathy.

2. Methods

The study was approved by the ethics committee in Canton Zurich. All participants received written and oral information and were requested to sign an informed consent statement.

2.1. Subjects. A convenience sample of 31 patients with diabetes Type 2 (with and without neuropathy) was recruited from the patients consulting the Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital of Zurich (Table 1). Patients were included if they were medically diagnosed with diabetes Type 2, were between 50 and 70 years of age, and had the ability to walk without assistive devices. Patients were excluded if they had concomitant foot ulcer, orthopaedic or surgical problems influencing gait parameters, a nondiabetic neuropathy (due to Charcot-Marie-Tooth disease, alcohol, or thyroid dysfunction), or neurological pathology influencing gait parameters.

Before gait analysis started, patients were assigned to one of three groups: "DIABETIC," "MILD NEUROPATHY," and "SEVERE NEUROPATHY" based on three tests. A Neurometer CPT electrodiagnostic device was used for sensory nerve conduction threshold (sNCT) evaluations at the great toe by determining current perception threshold (CPT) levels. CPT permits diagnosis of neuropathy due to its ability to diagnose and quantify hyperaesthesia [26]. The used Rapid Screening CPT (R-CPT) resulted in a value between 1 and 25, where the higher numbers indicate worse nerve conduction. The value was used to grade neuropathy: no neuropathy = 6–13, moderate neuropathy = 14–19, severe neuropathy = 20–25. The Rydel-Seiffer tuning fork test was used to assess the vibratory threshold perception at the base of the great toe as a good predictor for impairment of the vibratory senses and, therefore, also usable to diagnose neuropathy [27–29]. The Rydel-Seiffer tuning fork test acquires values between 0 and 8, where the higher values indicate better vibratory senses. Patients were grouped by the test in one of the three categories with application of an age-related correction [30]. The third test used was the Semmes-Weinstein monofilament test, a good test to diagnose but not to quantify neuropathy [31]. If the subjects did not notice five of seven stimuli, a neuropathy was diagnosed.

Testing and group assignment was performed by an MD unfamiliar with the study design and the patients. Based on the results of all three tests the MD categorized the patients in one of three categories. The MD principally considered the results from the Neurometer CPT/C tests where three values for every frequency were obtained for the right and the left great toe. If at least two frequencies of the worse foot had a value over 14, the subject was allocated to the "moderate neuropathy" group. If at least two frequencies of the worse foot had a value over 19, the subject was allocated to the "severe neuropathy" group. If there were any uncertainties in the group allocation according to R-CPT values, the Rydel-Seiffer tuning fork test was the next criteria considered. The loading of the group arrangement's criteria was Neurometer CPT/C > Rydel-Seiffer tuning fork > Semmes-Weinstein monofilament test.

After the analysis of nerve conduction the gait analysis started.

Table 1: Demographic description of the consecutively recruited subjects at baseline.

Subject (no.)	Sex (m/f)	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)	Group*
01	m	60	82	1.76	26.5	2
02	m	70	88	1.74	29.1	2
03	f	64	92	1.73	30.7	3
04	m	63	94	1.76	30.4	3
05	m	69	84	1.76	27.1	2
06	m	57	102	1.78	32.2	2
07	f	63	67	1.55	27.9	2
08	m	70	95	1.76	30.7	3
09	m	69	73	1.79	22.8	2
10	m	57	98	1.84	29	3
11	m	61	103	1.79	32.2	1
12	m	69	66	1.72	22.3	2
13	m	53	90	1.71	30.8	3
14	m	70	102	1.85	29.8	3
15	f	67	78	1.64	29	1
16	m	65	94	1.74	31.1	1
17	m	62	81	1.75	26.5	1
18	m	62	92	1.70	31.8	1
19	m	56	108	1.82	32.6	1
20	m	59	67	1.67	24	1
21	m	60	76	1.73	25.4	1
22	m	56	93	1.70	32.2	1
23	f	64	54	1.60	21.1	2
24	m	60	92	1.78	29.0	1
25	f	50	60	1.63	22.6	2
26	m	57	85	1.80	26.2	2
27	f	60	75	1.60	29.3	1
28	m	55	85	1.78	26.8	1
29	m	65	81	1.87	23.2	2

BMI: body mass index; * 1: "diabetic," 2: "mild neuropathy," and 3: "severe neuropathy"; m/f: male/female.

2.2. Apparatus. A triaxial accelerometer (DynaPort MiniMod, McRoberts BV, The Hague, The Netherlands) was used to measure pelvic accelerations. The accelerometer was placed at the lower back of the subject with the center of the device at the level of the second sacral vertebrae.

2.3. Test Procedures. Each subject was assessed during usual walking at preferred velocity under two different conditions over an outdoor gait therapy walkway with different surfaces: (1) silent walking on the walkway and (2) walking on the walkway with a counting task. The walkway contained a paved trajectory, cobble stones, and gravel rocks (Figure 1(a)). The complete walkway was 31 meter long and 1.5 meter wide. To measure steady state- walking, the 16.6 meters (with the three different surfaces) of the walking course was used as the test distance. The remaining parts of the walkway were used for acceleration and deceleration. At the end of the first 31 meters the subjects had to stop for two seconds, then turn around, and walk the walkway back to the starting point. At the beginning the measurement was started (S), and, at the end, the measurement was stopped (S + M5; Figure 1(b)).

(1) Test run with subject's preferred walking speed: the subject received the most important information: no speaking, hold arms out of the pocket, and try not to stop walking during the measurement.

(2) First trial with preferred walking speed: the subject was briefed to "*walk like you would bring a letter to the mailbox*" (single task).

(3) Second trial with preferred walking speed and an additional cognitive task (count backwards aloud in steps of three): the subject had to walk and count aloud in steps of three. The subject was briefed to "*try to walk and count at the same time. Do not favour one task over the other but try to perform these concurrently*" (dual task).

The dual task was subtracting repeatedly the number three starting from 200 down and was practiced before gait

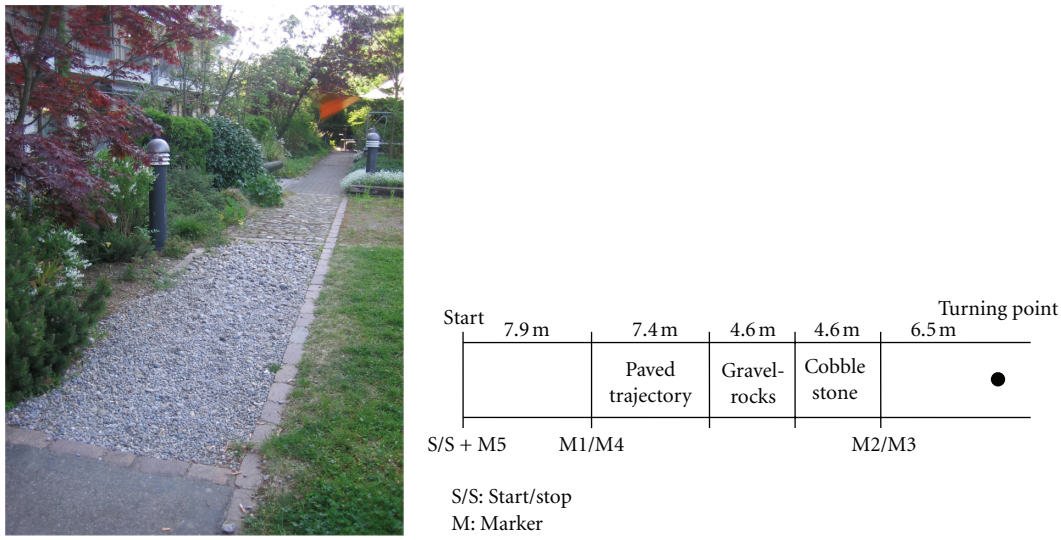


Figure 1: (a) The gait garden walkway with paved trajectory, cobble stones, and gravel rocks. (b) Schematic representation of the walkway and test procedure used. M signifies markers that are set in the signal to recognize the gait data for analyses.

testing while sitting on a chair. Subjects were told to try and perform both tasks at the same time without prioritizing either the walking or counting. A small receiver was mounted on the accelerometer and the researcher placed a marker in the data through triggering by the use of a remote control when the subjects passed distance lines (Figure 1(b)). The researcher walked alongside the subjects to ensure their safety. At the end of the last trial the SD card was removed from the accelerometer, and the measurements were checked for completeness on a laptop. The subject was asked to come again for the retest one week later at the same time and to wear the same shoes as during the first trial.

Per trial, all measured data between the two trigger signals (M1-M2/M3-M4) were used for analysis. Walking speed (V), cadence, mean values ($\overline{X}$) of step duration (SDu) and step length (SL), and corresponding standard deviations (SD) were calculated for each subject and each trial.

3. Statistical Analyses

Normality of the data was tested with the Kolmogorov-Smirnov test. Descriptive statistics were used to define the study population and to calculate gait characteristics.

We used the intraclass correlation ($ICC_{(2,1)}$) with 95% confidence intervals to calculate intervisit reliability between visit 1 and visit 2. $ICC_{(2,1)}$ was used because individual ratings constitute the unit of analysis, and raters and subjects were conceived as being a random selection. There was one week between visit 1 and 2. To interpret $ICC_{(2,1)}$ values we used benchmarks suggested by Shrout and Fleiss [32] (>0.75 excellent reliability, 0.4–0.75 fair to good reliability, and <0.4 poor reliability). To evaluate precision the 95% limits of agreement statistics (Bland and Altman) were used. It expresses the degree of error proportional to the mean, and was calculated as $\overline{d} \pm 2SD_{diff}$ [33, 34], where $\overline{d}$ is the mean of the difference and SD_{diff} the standard deviation of the difference. The measurement error (standard error of the mean difference (SEM)) was reported, and the smallest detectable difference (SDD) for each parameter was calculated as described by de Vet et al. [35]. SEM was derived by $\sigma\sqrt{(1 - ICC)}$ in which σ represents the total variance [36]. The smallest detectable change was calculated with the formula $1.96 \times SEM \times \sqrt{2}$.

To identify differences between groups we used an analysis with planned contrasts [37]. All statistical analyses were performed using SPSS 17 for Windows (SPSS Inc.).

4. Results

Of the 31 patients screened for eligibility all met the inclusion criteria. Data from two individuals were, however, not available. One person presented with hypersensibility of the feet and could not be measured. Technical problems prevented data acquisition for the second person. This resulted in complete data for 29 patients (21 male and 8 female) at baseline, mean age: 61.9 (±5.5) years; body mass index: 28.2 (±3.5)) kg/m^2; leg length 0.84 (±0.06) m (Table 1).

Twelve patients were categorized as "DIABETIC," eleven as "MILD NEUROPATHY," and six as "SEVERE NEUROPATHY." Post hoc ANOVA revealed that the groups did not differ in Age $F(2, 26) = 0.949$, $P = .40$; height $F(2, 26) = 1.26$, $P = .302$; SDu $F(2, 26) = 1.99$, $P = .157$; V $F(2, 26) = 3.01$, $P = .067$; cadence $F(2, 26) = 1.98$, $P = .159$ and showed to be different for weight $F(2, 26) = 4.729$, $P = .018$; BMI $F(2, 26) = 4.28$, $P = .025$; SL $F(2, 26) = 3.14$, $P = .048$.

Four patients were unable or refused to perform the retest due to time limitations or lack of motivation. For the reliability testing we had twenty-five patients performing retesting (17 male and 8 female); mean age: 61 (±5.7)

Table 2: Results of repeated measurements ($N = 25$).

	Test visit 1 mean ± SD	Test visit 2 mean ± SD	P value
Single task			
SDu (s)	0.54 (0.051)	0.55 (0.045)	0.771
SL (m)	0.69 (0.095)	0.69 (0.111)	0.884
V (m/s)	1.28 (0.213)	1.28 (0.243)	0.942
Cad (step/min)	111.7 (10.234)	111.0 (9.031)	0.652
Dual task			
SDu (s)	0.58 (0.079)	0.56 (0.056)	0.046
SL (m)	0.67 (0.109)	0.68 (0.107)	0.325
V (m/s)	1.17 (0.273)	1.23 (0.233)	0.154
Cad (step/min)	104.51 (12.626)	107.7 (10.170)	0.046

SD: standard deviation; SDu: step duration; SL: step length; V: velocity; Cad: cadence.

years; Body Mass Index: 28.7 (±3.5) kg/m^2, leg length 0.83 (±0.06) m. Eleven patients were "DIABETIC," eight "MILD NEUROPATHY" and six "SEVERE NEUROPATHY".

4.1. Differences between the Walking Conditions. Table 2 presents means and SDs of both tests. Significant differences between the two test conditions at baseline, single versus dual task walking, were identified for all gait parameters (walking speed: $t(28) = 3.616$, $P = .001$, cadence: $t(28) = 3.221$, $P = .003$, step duration: $t(28) = -3.112$, $P = .004$, and step length: $t(28) = 2.308$, $P = .029$. Walking speed, step length, and cadence were significantly decreased under dual tasking, and step duration was significantly increased compared to normal walking.

4.2. Reliability. All data were normally distributed and showed no heteroscedasticity. The results of the repeated measurements for the different gait parameters SDu, SL, V, and Cadence are presented in Table 2. Except for cadence under dual task condition there were no differences in walking between visit 1 and 2.

All gait parameters on the walking trajectory under single and dual task walking with regard to test retest reliability are illustrated in Figure 2 by Bland-Altman plots. The results of the test retest reliabilities are summarized in Table 3. The reliability of single task walking speed, cadence, step duration, and step length was "excellent" [32] (ICCs between 0.824–0.898 and SEMs between 0.03–5.2) and comparable to the reliability of dual task walking speed, cadence, step duration and step length (ICCs between 0.826–0.869 and SEMs between 0.1–5.38).

4.3. Validity. The mean values and standard deviations of the gait parameters of 29 evaluated patients at baseline are reported in Table 4 for their grouping. Planned contrasts showed that there was no significant effect on SDu, V, and cadence and a significant effect of grouping on step length performance. This latter parameter, however, showed a large effect [38]. The planned contrasts revealed that having mild and severe PN did not significantly alter step length compared to diabetic patients presenting without PN, $t(26) = -1.318$, $P = .101$, and having severe PN significantly influenced step length compared to mild PN, $t(26) = -2.469$, $P = .046$ (one tailed).

5. Discussion

This study has shown that the reliability of walking speed, cadence, step duration and step length on different surfaces and under dual task conditions was high with excellent ICCs, small SEMs and RLOAs in older adults with diabetes using the DynaPort MiniMod system. Results from discriminant validity were essentially non conclusive, with the exception of step length. There are, therefore, only indications that the system might also be able to distinguish between subpopulations within the population of patients with diabetes based on step length. The disease status of the elderly participants in our study varied from having diabetes without PN and having diabetes with mild or severe polyneuropathy. We thus expected our subjects to represent a heterogeneous group with regard to walking abilities. From previous studies we know that disease severity negatively influences walking velocity [4] especially in challenging environments where patients with neuropathy walk slower when compared to patients without neuropathy [12]. We think that the negative findings in our cross-sectional sample are very likely related to the limited statistical power of this analysis and might be attributed to a possible Type I error. A post hoc power analysis revealed that Power (1-β err prob) = 0.19. Our data allow for an a priori sample size calculation for a future trial with a fixed effects one-way ANOVA design and under the assumption of a moderate effect size of 0.25. To avoid a type I or II error in this future trial, we need an estimated sample size of 159 (53 individuals per group). This would result in 80% power at α-level 0.05 [39].

The gait changes that we observed in dual task walking relative to single task walking are consistent with other studies that demonstrate that cognitive tasks have a destabilizing effect on gait [40–44]. This finding seems to indicate that it is important to consider additional cognitive tasks in gait assessment of diabetic patient populations in clinical practice.

There is scarce information available about the reliability of body fixed sensor approaches to assess gait parameters in older adults with diabetes. The ICCs for walking speed and cadence that we found were, however, similar to values reported by Allet et al. [19] who were using the Physilog system in older, diabetic subjects.

The relative reliability is the degree to which individuals maintain their test results in a sample with repeated measurements and is affected by sample heterogeneity, that means the more heterogeneous a sample is, the higher the relative reliability becomes. Therefore, a high correlation may still mean unacceptable measurement error for some analytical goals, for example, for individualised assessments [36], and data about absolute reliabilities of a test are desired for clinical use. The determination of what constitutes an acceptable RLOA depends on what size difference the researcher

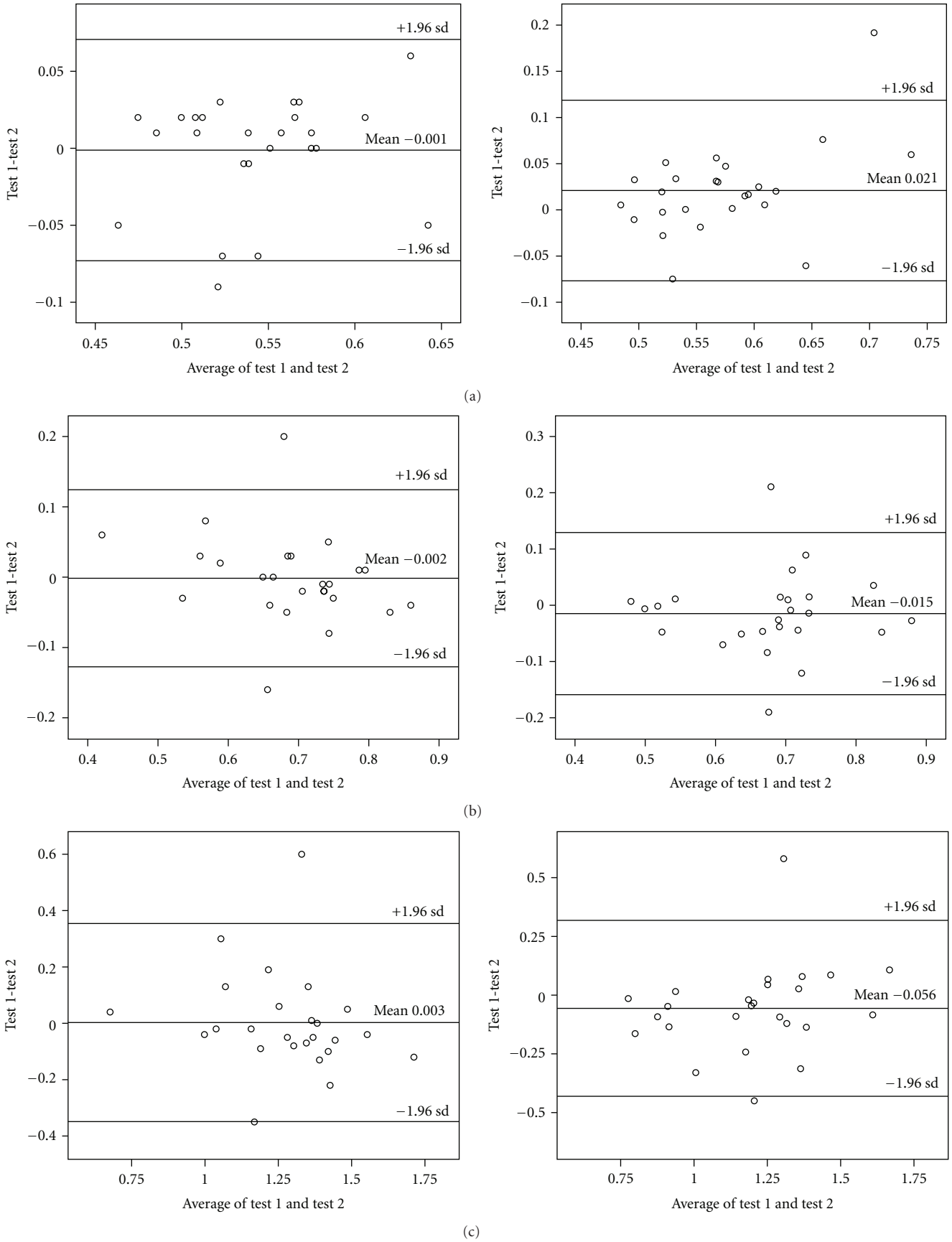
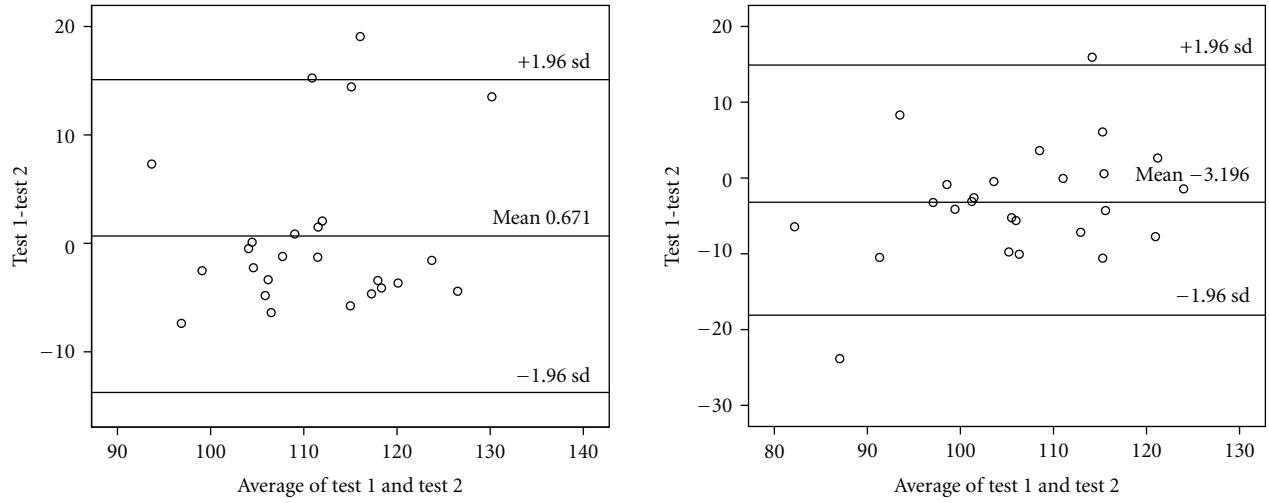


Figure 2: Continued.



(d)

Figure 2: Bland-Altman plots of (a) step duration, (b) step length, (c) walking velocity, and (d) cadence (top to bottom). Left side represents the single task condition, and the right side represents the dual task walking.

Table 3: Reliability of different gait parameters[a] at preferred speed (ICC: intraclass correlation coefficient, CI 95% confidence interval 95%, SEM standard error of measurement, SDD smallest detectable difference, and LALB limits of agreement lower boundary, LAUB limits of agreement upper boundary).

	ICC	CI 95%	SEM	CI 95%	SDD	LALB	LAUB
Single task							
SDu (s)	0.848	0.652–0.933	0.03	±0.06	0.09	−0.072	0.071
SL (m)	0.898	0.767–0.955	0.04	±0.09	0.12	−0.128	0.124
V (m/s)	0.824	0.597–0.923	0.12	±0.25	0.35	−0.349	0.354
Cad (step/min)	0.834	0.623–0.927	5.20	±10.2	14.42	−13.754	15.096
Dual task							
SDu (s)	0.829	0.597–0.926	0.10	±0.20	0.28	−0.077	0.119
SL (m)	0.869	0.706–0.942	0.17	±0.34	0.48	−0.159	0.130
V (m/s)	0.829	0.616–0.924	0.13	±0.26	0.37	−0.431	0.318
Cad (step/min)	0.826	0.672–0.940	5.38	±10.54	14.90	−18.101	14.901

SDu: step duration; SL: step length; V: velocity; Cad: cadence.
[a]Calculations—SEM: $\sqrt{\text{Mean square error}}$; CI 95% = $\pm 1.96 \times$ SEM; SDD = $1.96 \times \sqrt{2} \times$ SEM.

Table 4: The mean and standard deviations of the gait parameters of 29 evaluated patients, grouped based on disease status, at baseline.

Performance measure	Group		
	Diabetic ($n = 12$)	Mild neuropathy ($n = 11$)	Severe neuropathy ($n = 6$)
Single task			
Step duration (SDu; s)	0.56 ± 0.03	0.53 ± 0.05	0.55 ± 0.05
Step length (SL; m)	0.72 ± 0.06	0.73 ± 0.1	0.62 ± 0.12
Velocity ($m \cdot s^{-1}$)	1.29 ± 0.14	1.39 ± 0.14	1.14 ± 0.37
Cadence (steps/min)	107 ± 5.8	115 ± 10.2	107.6 ± 15
Dual task			
Step duration (SDu; s)	0.6 ± 0.08	0.55 ± 0.05	0.6 ± 0.12
Step length (SL; m)	0.7 ± 0.07	0.7 ± 0.13	0.63 ± 0.1
Velocity ($m \cdot s^{-1}$)	1.18 ± 0.21	1.31 ± 0.28	1.09 ± 0.32
Cadence (steps/min)	101.4 ± 11	110 ± 9.3	103.4 ± 17.6

or clinician wants to detect when comparing groups or when assessing the effect of interventions [45]. Whether the absolute reliability reported here for the gait measures is sufficiently high to identify gait impairments or small effects of an intervention program to improve walking in populations suffering from diabetes should be part of future studies. In particular, the RLOAs for step length and gait velocity might be indicative for rather large needed changes to be detected with the system. A study that investigated gait recovery in a sample of patients with diabetes due to specific exercises [46], with a mean age of 63 years and that used the Physilog gait analysis system for evaluation in challenging environments, showed that changes in gait velocity of around $0.149\,\mathrm{m}\cdot\mathrm{s}^{-1}$, and improvements of 10% for cadence are achievable with specific rehabilitation [5, 6]. Whether such changes are also clinically meaningful should be determined in future studies.

In the present study we have shown that step length measures derived from the DynaPort MiniMod are significantly different between groups of patients. There are measurable differences between individuals with mild and severe PN. Clinical detection of these differences potentially allows the division of diabetes patients into two groups with different mean step length: one with severe NP and one without severe NP. These results support the assertion that there is a relationship between quality of walking and the presence of PN. However, these are only preliminary data, and further (cross-sectional and longitudinal) research is needed with larger samples to substantiate this observation.

To obtain the diagnostic information from a walking test in a challenging environment alone, the outcomes of the gait analysis should be compared with other diagnostic tests in use. This necessitates the concurrent measurement of those tests in future research. Therefore, bigger samples of subjects should be selected in the future, and with logistic regression analysis the contribution of the DynaPort MiniMod gait assessment to existing diagnostic tests should be estimated more precisely [47].

6. Conclusions

The results of this study demonstrate that walking speed, cadence, step duration, and step length under more challenging conditions can be reliably measured in adults with diabetes using the DynaPort MiniMod system. There are first indications that the system is able to discriminate subgroups of patients with diabetes based on their step length. Further research in diabetic populations is needed to determine the value of these parameters that are derived from this measurement system in clinical settings.

Acknowledgments

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Clinical Study

Plantar Temperature Response to Walking in Diabetes with and without Acute Charcot: The Charcot Activity Response Test

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Objective. Asymmetric plantar temperature differences secondary to inflammation is a hallmark for the diagnosis and treatment response of Charcot foot syndrome. However, little attention has been given to temperature response to activity. We examined dynamic changes in plantar temperature (PT) as a function of graduated walking activity to quantify thermal responses during the first 200 steps. *Methods*. Fifteen individuals with Acute Charcot neuroarthropathy (CN) and 17 non-CN participants with type 2 diabetes and peripheral neuropathy were recruited. All participants walked for two predefined paths of 50 and 150 steps. A thermal image was acquired at baseline after acclimatization and immediately after each walking trial. The PT response as a function of number of steps was examined using a validated wearable sensor technology. The hot spot temperature was identified by the 95th percentile of measured temperature at each anatomical region (hind/mid/forefoot). *Results*. During initial activity, the PT was reduced in all participants, but the temperature drop for the nonaffected foot was 1.9 times greater than the affected side in CN group ($P = 0.04$). Interestingly, the PT in CN was sharply increased after 50 steps for both feet, while no difference was observed in non-CN between 50 and 200 steps. *Conclusions*. The variability in thermal response to the graduated walking activity between Charcot and non-Charcot feet warrants future investigation to provide further insight into the correlation between thermal response and ulcer/Charcot development. This stress test may be helpful to differentiate CN and its response to treatment earlier in its course.

1. Background

Charcot neuroarthropathy (CN) is a devastating complication of diabetes. It has a similar mortality rate as lower extremity ulceration and a twofold higher rate of major amputation compared to those without CN [1]. It has been estimated that 63% of CN patients will develop a foot ulcer [2]. The combination of foot ulcer and CN increases the risk of amputation 12-fold [3]. The increased mortality risk associated with CN appears to be independent of foot ulcer and other comorbidities [2].

What further complicates CN is that there is no clear definition for it [4]. There are no pathologic markers or diagnostic criteria. Therefore, the diagnosis relies on pattern recognition and clinical intuition [5]. Not surprisingly, the diagnosis can be missed up to 95% of the time [6] and the average diagnostic delay has been estimated at almost 7 months [7].

A significant number of CN patients either present or subsequently develop bilateral Charcot foot. A weighted average of studies reporting bilateral involvement suggests 21% (range 9%–75%) of CN patients will present or subsequently develop Charcot foot [8–14]. Of those studies reporting subsequent development of CN, point estimates for bilateral involvement ranged from 2 to 3.3 years (range 1–6 years) after initial presentation. However, 21% of cases presented at baseline are with bilateral involvement [8, 10, 14]. This suggests a window of opportunity for the prevention of bilateral CN development. Certainly, a goal for identifying CN earlier is an important diagnostic pursuit, as well.

The role of thermometry in the detection of CN has been well described [8, 15, 16]. Armstrong and Lavery reported baseline infrared dermal thermometry results for 39 patients presenting with unilateral acute CN [15]. After 15 minutes' rest, they found an average 8.8 ± 2.3°F (~4.9 ± 1.3°C) difference in temperature compared to the contralateral joint of interest (JOI). In a separate study, the same team reported specific mean joint differences of 7.3°F (~4.1°C), 8.0°F (~4.4°C), and 8.8°F (~4.9°C) for the ankle Chopart and Lisfranc's joint, respectively [16]. Temperature differences correlate highly with radiographic changes [15] and with markers of bone turnover [17]. Offloading treatment should continue until temperature equilibration with the contralateral JOI [15] or within 2°C [18] is achieved. It is, however, unclear how temperature gradients changes are considered as a function of activity level. In this study, we examined temperature gradient changes of plantar temperature as a function of number of steps in patients with type 2 diabetes and peripheral neuropathy (DPN) including with and without acute CN.

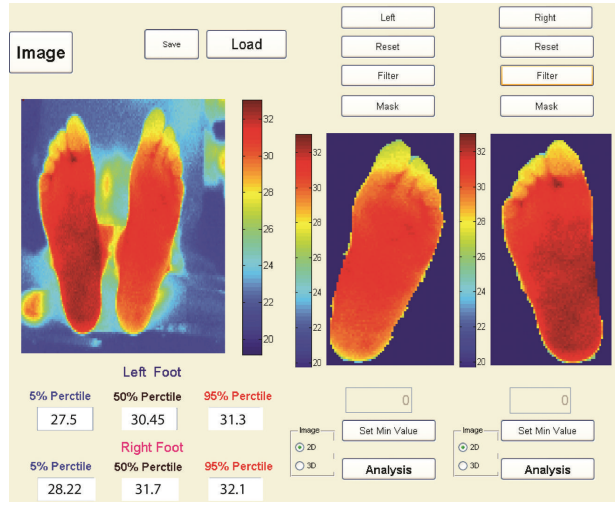

Figure 1: A purpose-designed image processing toolbox was developed using Matlab (version 7.4, The MathWorks, Inc., Natick, MA, USA), to isolate each foot from the thermal image and extract plantar temperature in three anatomical regions of foot including hind-, mid-, and forefoot.

2. Research Design and Methods

The study was conducted at a single academic medical center as part of a multinational collaborative study of lower extremity disease in diabetes. The study received ethical approval; participants were informed of the nature of the study and signed an informed consent form. Participants were included if they had type 2 diabetes diagnosed by their primary care physician and exhibited loss of protective sensation using 10-gram monofilament at 1–3 sites in the following locations: hallux, 1st, 3rd, and 5th metatarsal heads [19]. Patients with major foot amputation and inability to walk a distance of 100 m without assistance were excluded. The diagnosis of unilateral acute CN was made by a single clinician using previously described clinical criteria of swelling, redness, and local temperature gradient [20–22].

All participants walked for two predefined paths of 50 and 150 steps (total 200 steps). A validated wearable gait analysis technology (LEGSys, Biosensics LLC, MA, USA) [23–25] was used to assess gait and quantify the number of steps. All subjects were examined in prescribed footwear. In CN patients, this included nine with removable cast walkers, one with surgical sandal, and five with prescribed shoes. A thermal camera (Fluke Co., Model i25) was used to monitor plantar temperature at baseline after foot acclimatization and immediately after each walking trial. The subject was asked to sit in a podiatric examination chair with their legs parallel to the transverse plane and their shoes and socks removed for a 5-minute environment acclimatization period for baseline assessment. This was done to allow the subject's feet to equilibrate to room temperature. All subsequent thermal images (approximately at 50 steps and 200 steps) were taken with shoes and socks removed immediately after each walking trial. Due to the intermittent measurement at 50 steps, there was a slight delay (approximately 30 seconds) between continuation of the subsequent walking trial. We assumed that the change in plantar temperature is not rapid and thus this delay should have a negligible effect on assessing plantar temperature.

A custom image processing toolbox (Figure 1) was designed using MATLAB version 7.4 (R2007z) (The MathWorks, Inc., Natick, MA, USA), to automatically isolate each foot from the thermal image using an edge detection algorithm. The toolbox also afforded manual enhancement and noise removal prior to the analysis. This is critical to accurately identify inflammatory hot spots and measure dynamic changes in plantar temperature. Using an automated masking algorithm, plantar temperature changes were measured in three independent anatomical regions (hind/mid/fore-foot). We estimated the 5th, 50th, and 95th temperature percentiles at each region. For the purpose of this study, only the 95th percentile value representing a hot spot was reported.

Paired sample Student's t-test was used to examine intra-subject PT differences between feet. A two-sample Student's t-test assuming equal variance was used between groups. ANOVA test (N-way analysis of variance) with linear model was used to examine the dependency of PT change on footwear type, gender, age, and active diabetic foot ulcer (DFU). Statistical significance was set at 0.05.

3. Results

Thirty-two eligible subjects (age: 56.6 ± 8.6 years, BMI = 30.3 ± 4.9 Kg/m^2, 87% male) were recruited. Fifteen subjects were diagnosed with CN and 17 as non-CN. Eight CN and nine non-CN participants had DFU. Nine CN participants wore casts, one sandal, and five wore prescribed shoes. Eight non-CN participants wore their habitual shoes, six wore prescription shoes, and three wore surgical sandals. At baseline, CN demonstrated a significant 1.84 ± 1.3°C

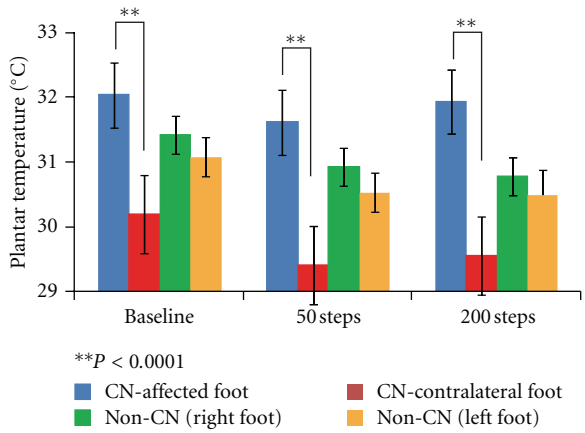

Figure 2: Plantar temperature in hot spot recognized in the midfoot region.

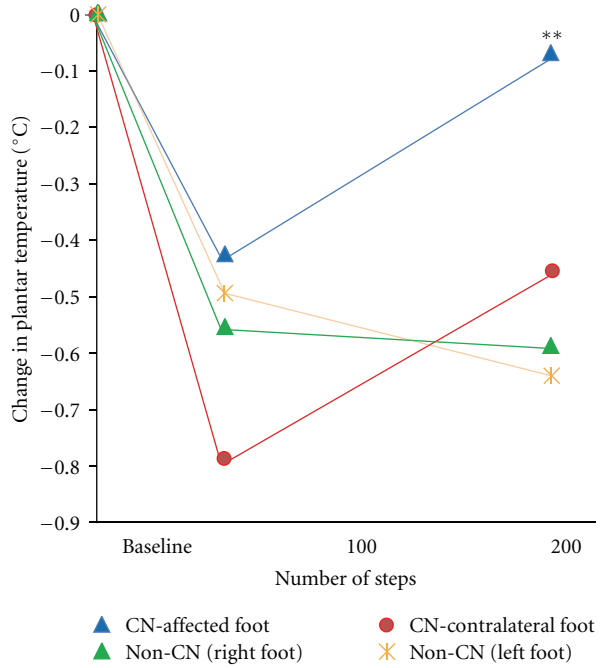

Figure 3: Change in plantar temperature as a function of walking steps for the hot spots recognized in the midfoot region.

difference ($P < 0.0001$) between the feet at JOI and for all plantar regions (Figure 2). No significant difference was observed in non-CN ($P > 0.3$). Upon activity initiation, plantar temperature was reduced in all participants, but the drop for nonaffected foot as well as non-CN was significantly lower by a factor of 1.9 than the affected side ($P = 0.04$). Interestingly, plantar temperature in CN was sharply increased by prolong walking beyond of 50 steps with slope of 0.25 deg/100 steps for both feet, while no difference was observed in non-CN between 50 and 200 steps ($P > 0.5$, Figure 3). At 200 steps, plantar temperature on the CN side was still higher than the contralateral foot and non-CN ($P < 0.0001$).

Multivariable analysis suggested PT asymmetry measured at baseline as well as after each walking trial is independent of DFU, gender, age, and type of footwear ($P > 0.1$) but significantly dependent on presence of CN ($P < 0.0001$). Using PT gradient criteria based on the JOI, the effect size between CN and non-CN group was increased by 61% at 50 steps compared to baseline ($d = 1.20$ and $r = 0.52$ at baseline versus $d = 1.94$ and $r = 0.70$ at 50 steps).

4. Discussion

The current study reports a simple objective method to characterize asymmetry in plantar temperature as a function of graduated walking activity. This technique characterizes the PT hot spot (95th percentile) at each plantar region instead of manual comparison of plantar temperature between two feet.

We found that all participants experienced initial temperature decrease in both feet after 50 steps. But the slope of PT cooling to baseline was significantly slower in the affected foot. Consequently, the temperature difference between CN affected and contralateral foot is magnified after walking 50 steps ($d = 1.20$ and $r = 0.52$ at baseline versus $d = 1.94$ and $r = 0.70$ at 50 steps).

The initial drop in plantar temperature in early-walking steps may be due to regulation of microvascular flow in response to cyclic loading and relaxation. Silver-Thorn [26] by applying a cyclic loading and unloading to human healthy tissue demonstrated that skin perfusion is initially increased in response to early loading and dropped with further increases in pressure or prolong loading till reaching to a steady-state level (first pulse response). Then, again it is increased followed by decreasing to the initial value in response to unloading (second pulse response or hyperemia response), whereas little to no tissue reperfusion was observed during prolong relaxation period without cyclic stress. Therefore, cyclic activities like walking may actually increase the cumulative plantar skin perfusion as a function of time (or time integral) compared to prolong relaxing (e.g., sitting, lying, and offloading) or prolong loading (e.g., standing) conditions. Thus, this skin perfusion regulation in response to cyclic stress may explain the initial drop in plantar temperature in early steps compared to baseline (relaxation) for healthy skin when other factors contributing to increase in skin temperature (e.g., friction, metabolic cost, etc.) are still negligible. Considering that the most of walking episodes are short (often less than 50 steps per episode) [27], this regulation mechanism is of key importance in regulating foot temperature during activity of daily living. A failure in the above-explained skin perfusion regulation in response to cyclic plantar stress may explain the lack of drop in temperature in the CN-affected foot.

In non-CN, the temperature remained the same after continued activity from 50 steps up to 200 steps, but temperature was lower relative to the temperature at baseline. In CN, there was, however, a significant increase in temperature at 200 steps compared to 50, significantly higher than temperature difference between 50 and 200 steps in non-CN. These interesting findings merit further study as a potential

stress test for prediction of unilateral or bilateral CN and subsequent ulcer development.

The sharp increase in plantar temperature in CN group after continued activity beyond 50 steps could be explained by a complex interplay between local metabolic status [28, 29], propensity for an ill-defined inflammatory overreaction [5, 29], perfusion status [30], the physical state of plantar tissue, and limited joint mobility which may increase skin friction or metabolic cost. There could be an empiric support for these findings from Johnson, who reported a sharp increase in plantar temperature in Charcot patients and postulated that it could be explained by hyperemia in Charcot foot [31]. According to Boulton et al., "It has been theorized that the site of pathology was within the arteriovenous shunts, which normally are under control of the sympathetic system. Loss of this function will result in blood being routed rapidly to the venous side of the capillary bed, increasing the local pO2, thereby decreasing the distal perfusion to the cells" [32]. These results also support that modulating duration of continuous steps and/or prolong standing during daily activity could be helpful for reducing the trauma in patients with CN or DFU [27, 33–35].

The temperature differences in our study differ from others at baseline [15, 16]. This could be due to the duration of acclimatization, use of a thermal imager as opposed to an infrared dermal thermometer, and aggregation of temperature into regions of the foot as opposed to manual point testing. Additionally, we have eliminated any bias towards absolute temperature measurements by using the 95th percentile values.

This study has few limitations. First, we were not able to control the stage of Charcot foot development. It is likely that some patients were in a coalescence phase. The magnitude of the differences between groups merit further investigation in stages 0 and 1 patients. It is entirely plausible that these patients are likely to have a higher thermal gradient. Second, we did not standardize the offloading footwear and, while our population was easily robust enough to assess temperature gradient, it was not sufficiently powered to perform a stratified analysis by stage and offloading footwear type. Third, due to limitations in technology, a short delay was required for assessing plantar temperature after each walking path. However, since the change in plantar temperature is not rapid, we assumed that the effect of this delay (approximately 30 seconds) for assessing change in plantar temperature as a function of walking is negligible. Another study should be addressed to validate this hypothesis.

The observed differential thermal response to walking initiation between Charcot and non-Charcot feet warrants future investigation to provide further insight into the correlation between activity dosing and thermal response. It may also lend valuable insight into identifying an "inflammatory trigger" that may ultimately provide an early-warning sign [36] or increased sensitivity for subsequent unilateral or bilateral CN development or clinical expression of foot ulcer. The importance of improved sensitivity and earlier diagnoses of CN was recently described by Wukich and colleagues. In their retrospective review of 22 CN patients, they emphasized the importance of identifying and aggressively treating stage 0 patients [6]. This was defined as patients with diabetes-related sensory neuropathy presenting following foot and ankle insult with local swelling, redness, and warmth and radiographic signs absent for fracture and normal alignment [37, 38]. The group that was identified and treated for 4 weeks developed significantly less complications (14%) versus the group that was identified and treated after 8 weeks (67%) [6].

In conclusion, the variability in thermal response to the initiation of walking between Charcot and non-Charcot feet warrants future investigation to potentially provide further insight into the correlation between thermal response and ulcer/Charcot development.

Authors' Contribution

B. Najafi researched data, wrote the paper, reviewed/edited the paper, contributed to discussion; G. Grewal recruited the subjects and analyzed the data. R. Menzies and T. Talal screened and recruited patients and, assisted in data collection, and contributed to discussion. M. Zirie contributed in discussion, J. Wrobel reviewed/edited researched data, wrote the paper, reviewed/edited the paper; contributed to discussion and D. G. Armstrong researched data, reviewed/edited the paper, and contributed to discussion.

Conflict of Interests

The authors declared no conflict of interests.

Acknowledgments

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Review Article

Transmetatarsal Amputation: A Case Series and Review of the Literature

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Foot ulceration is a major cause of morbidity amongst patients with diabetes. In severe cases of ulceration, osteomyelitis and amputation can ensue. A distinct lack of agreement exists on the most appropriate level of amputation in cases of severe foot ulceration/infection to provide predictable healing rates. This paper provides an overview of the transmetatarsal amputation (TMA) as a limb salvage procedure and is written with the perspective and experiences of the Department of Podiatric Surgery at West Middlesex University Hospital (WMUH). We have reflected on the cases of 11 patients (12 feet) and have found the TMA to be an effective procedure in the management of cases of severe forefoot ulceration and infection.

1. Introduction

In recent times, increased attention has been placed on the alarming increase in the incidence of diabetes. Diabetic foot ulcers occur in up to 15% of diabetic patients [1], and amputation rates amongst this population have been documented as 11% [2]. In particular cases of severe foot infection, amputation should not necessarily be looked upon as failure of care, but rather the most appropriate intervention for preventing more proximal spread and persistent hospital attendance. Aggressive management of severe foot infection/ulceration can reduce the risk of proximal amputation.

2. Transmetatarsal Amputation

A proportion of the diabetic community experience serious and debilitating complications associated with their feet, with a 12–25% increased risk of developing foot ulceration [3]. Development of diabetic foot ulceration is often a multifactorial process; however, the presence of influences such as neuropathy and peripheral vascular disease is recognised as significant contributing factor. The neuroischaemic ulceration accounts for 90% of those encountered in the diabetic population [4], and approximately half of diabetic foot wounds develop an infection, the majority involving only soft tissue [5]. In circumstances where soft tissue infection is severe or where underlying bone is infected, amputation may be considered an appropriate line of treatment. Mills et al. [6] recognised that infection and gangrene due to microvascular disease were two major factors that resulted in failure of wound healing, resulting in amputation.

At WMUH, a treatment pathway has been developed for patients with severe foot ulceration/infection who have been deemed suitable candidates for undergoing TMA (see Assessment and Treatment below). Patients are urgently admitted into the hospital and are assessed by the medical and surgical teams, often with input from the tissue viability nurses. The treatment regime is implemented and a significant effort is made to bring the patient on board with the treatment plan. We believe this to be an important factor in improving compliance with the intention of maximising the likelihood of a satisfactory outcome.

Assessment

(i) Medical team assessment and management:

(a) stabilisation glycaemic control +/− insulin sliding scale,

(b) stabilisation of level of infection via antimicrobial therapy based on clinical presentation and hospital guidelines on diabetic lower limb infection,

(c) close monitoring of patient's C-reactive protein, full blood count, temperature, and blood sugar.

(ii) Surgical team assessment:

(a) determination of extent of infection,

(b) assessment of vascular status,

(c) assessment of viable soft tissue.

(iii) Investigations: glycated haemoglobin, C-reactive protein, differential white cell count, culture and sensitivity, doppler, and X-ray.

Treatment

(i) Maintenance of stabilised glycaemic control.

(ii) Decompression of infected tissue:

(a) incision and drainage where necessary,

(b) deep swabs with culture and sensitivity with appropriate modifications to antibiotic therapy where necessary,

(c) negative pressure wound therapy.

(iii) Monitoring of level of infection and determination of healing potential.

(iv) Transmetatarsal amputation with adjunctive soft tissue procedures.

(v) Orthotist-rocker-bottom shoes with total contact insert.

(vi) Discharge when deemed appropriate.

The aim in all cases of diabetic foot infection is to maintain foot function and preserve structure. However, in certain cases, where the soft tissue envelope has been lost or where infection or circulatory impairment has rendered the forefoot nonviable (Figure 1), a transmetatarsal amputation (TMA) might be considered an appropriate option.

A TMA involves removal of the forefoot at the level of the metatarsal shafts with the aim of maximising limb function by maintaining a significant portion of the foot. The procedure was first described by Bernard and Heuto [7] for the treatment of trench foot and was later popularised by McKettrick and colleagues [8] as a limb salvaging procedure used for severe diabetic foot complications. The TMA is considered preferable to amputation through the hindfoot or traditional below knee amputation (BKA) and is generally accepted as an effective salvage procedure in cases of forefoot infection, gangrene, and chronic ulceration. The primary advantage is the preservation of a viable weight-bearing platform allowing early ambulation, thus enabling the patients to maintain their independence, whilst maintaining a more acceptable appearance as it may be disguised somewhat with footwear. A partial foot amputation also results in less expenditure of energy during ambulation than more proximal amputations, facilitating mobility and independence [9]. Compared to more proximal amputations, the procedure proves to be the most favourable option with regard to patient satisfaction and function [10].

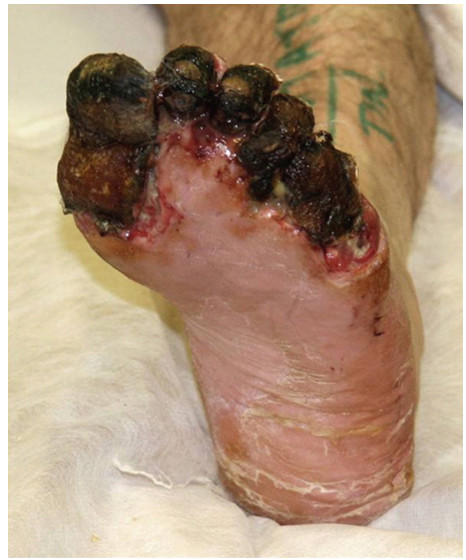

Figure 1

Table 1 illustrates eleven patients (twelve feet) between June 2006 and December 2011 who have undergone a transmetatarsal amputation under our care. Case J was a nondiabetic case that presented with bilateral forefoot ischaemia as a result of frostbite and underwent bilateral TMA.

All patients remain in hospital until we are satisfied that their recovery is progressing in a satisfactory manner and that domestic circumstances are suitable and appropriate for home discharge. Keeping these high-risk patients in hospital for a longer period immediately postoperatively increases compliance and has, in our experience, lowered readmission rates and further surgery including more proximal amputation.

3. Reducing Complications

Complications are not uncommon following TMA. Anthony et al. [11] reported that 82% of patients who underwent this procedure required further surgery due to postoperative complications, with Pollard and colleagues [12] reporting the need for a more proximal amputation in 32% of cases and hospital mortality (within 30 days of TMA) of 1.98%. These results highlight the need to address factors likely to cause or contribute to subsequent tissue breakdown.

None of our cohort died within 30-days of their amputation, and only one went on to require a BKA. It must be noted that this is a smaller number of patients in comparison to those previously quoted. This 30 day survival rate betters that of those requiring more proximal amputation with up to 3.6% of BKA patients deceased due to cardiac disease within

Table 1

Patient	Age/sex at time of TMA	Diabetes	Date of TMA	Adjunct procedures	Current status
A	62/M	Type II	05/06/06	STATT, GR	Healed
B	40/M	Type II	04/08/06	Popliteal bypass, BKA	Deceased
C	57/M	Type I	23/11/07	STATT, GR	Healed
D	64/M	Type II	08/09/08	I&D	Healed
E	50/M	Type II	18/10/08	Pan talar fusion scheduled	Deceased
F	47/M	Type I	02/02/09	STATT, GR	Healed
G	46/M	Type I	07/05/07	Skin graft, I&D, STATT, GR	Healed
H	56/F	Type I	16/03/09	STATT, GR	Healed
I	51/M	Type I	27/04/09	STATT, GR, I&D	Healed
J	46/M	Nondiabetic	11/02/10	STATT, GR	Healed
K	46/F	Type II	16/12/11	STATT, GR	Healed

STATT: split tibialis anterior tendon transfer; GR: gastrocnemius recession; BKA: below knee amputation; I&D: incision and drainage.

30 days [13]. 81% of the patients in this retrospective study had a history of diabetes; however, this was not shown to be a significant predictor of perioperative 30-day mortality. The evidence from the literature illustrates how average survival following major amputation decreases as the level of amputation is sited more proximally. Average survival was noted as 52 months and 20 months for BKA and AKA, respectively. It must be taken into consideration, however, that patients requiring more proximal amputation often have a greater degree of pathology and comorbidities, which would go some way to explaining higher mortality rates.

One of the most significant and well-documented problems with the TMA is the difficulty in predicting successful wound healing. To minimise the likelihood of further tissue breakdown, a number of issues may need to be addressed.

Incision planning is crucial in both providing necessary surgical exposure and also maximising the use of viable soft tissue. A fish-mouth incision is made as distally as possible to maintain as much length to the foot as possible and ensure an adequate plantar flap can be brought dorsally providing soft tissue protection for the metatarsal ends. With the metatarsal heads exposed, clear visualisation of the metatarsal parabola is possible and this allows for the pattern to be maintained when resecting the distal portions of the metatarsals (Figure 2). We aim to maintain the metatarsal parabola in an attempt to prevent peak pressure points on the stump caused by a prominent metatarsal distally. Avascular structures such as tendon stumps and the metatarsophalangeal joint plantar plates are resected as these can pose a nidus for infection.

Amputation at the level of the metatarsals causes muscular imbalance with resultant equinovarus deformity due to unopposed action of gastrocnemius, tibialis anterior, and tibialis posterior with the loss of extensor hallucis longus and extensor digitorum longus. This is addressed by performing a gastrocnemius lengthening and a split tibialis anterior tendon transfer (STATT). The STATT involves detachment of the lateral half of the tibialis anterior tendon at its insertion through an initial incision on the dorsomedial aspect of the foot. An incision is made on the anterior aspect of the lower leg and tibialis anterior is identified. The lateral portion of the tendon is passed under the extensor retinaculum to the proximal incision causing a longitudinal split in the tendon. This section of the tendon is then redirected distally and laterally back under the extensor retinaculum to a third incision on the dorsolateral aspect of the foot and is attached to the lateral cuneiform with a bone anchor suture. This allows the foot to sit in a plantigrade fashion in an attempt at reducing peak pressures along the lateral border of the foot (Figure 3).

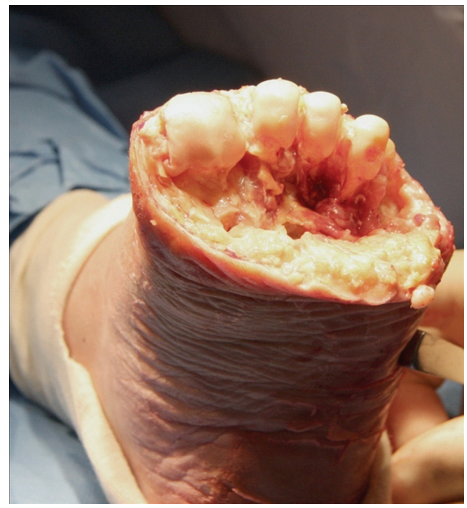

Figure 2

This procedure was routinely carried out except in the case of Patient G. Following delayed healing and a split thickness skin graft at the amputation site, a decision was made not to subject the foot to further surgical insult. We hoped to provide palliative protection in an attempt to prevent further breakdown; however, the patient went onto suffer further ulceration due to subsequent equinovarus deformity. The patient subsequently underwent the aforementioned soft tissue procedures and to date has had no further ulceration or surgery on this foot.

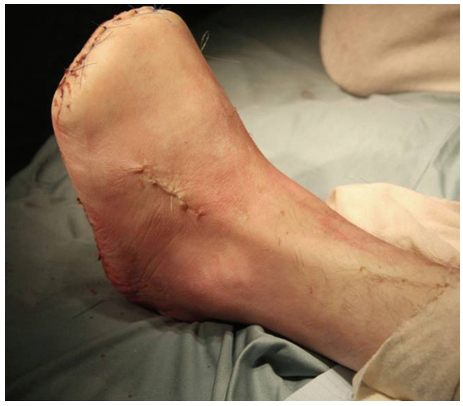

Figure 3: Not the visible tibialis anterior tendon routed laterally following a STATT.

Tendo Achilles lengthening (TAL) has been shown to effectively reduce peak plantar pressures in the forefoot [14]. La Fontaine et al. [15] alluded to the fact that TAL, although useful, does have its own associated complications such as tendon rupture, heel ulceration, and recurrence of ankle equinus. The senior surgeon in our department (MT) prefers an open gastrocnemius recession, as this procedure is simple to perform with few complications in comparison to the Triple Hoke TAL. Gastrocnemius is well vascularised in comparison with the Achilles tendon and therefore should heal in a more predictable fashion with less chance of tendon rupture. Additionally, where tightness of soleus is not an issue with adequate dorsiflexion at the ankle possible with the knee flexed, lengthening of the Achilles may be seen to unnecessarily weaken the gastrocnemius-soleus complex. Gastrocnemius recession has also been shown to result in superior push-off power with lesser risk of recurrence of equinus in comparison to TAL in cerebral palsy patients [16, 17].

In instances of vascular insufficiency, revascularisation procedures may be required. Predicting the likelihood of successful wound healing depends largely on the patency of the vascular supply and many tests are available to aid in determination of vascular status. Ankle brachial pressure indices (ABPIs) are inexpensive and easy to perform but not necessarily a predictor of healing [18]. Vascular compromise is often masked by calcification of arteries and therefore interpretation of ABPI results should be made with caution. Other physiological tests of wound healing potential such as transcutaneous oxygen pressure and skin perfusion pressure have been reported with encouraging prediction rates following amputation [19, 20]. When significant vascular impairment is encountered, the opinion of the vascular team is sought in the hope that they can improve the patency of blood supply. Revascularisation procedures; however, are not always a viable solution to vascular disease. Patient B underwent a failed popliteal bypass due to the absence of viable arteries in the lower leg and subsequently required a BKA as a result of advanced peripheral vascular disease. In this case, the patient was particularly keen to avoid a knee level amputation and a TMA was agreed upon with significant emphasis placed upon the poor prognosis. In hindsight, a BKA would have been a more appropriate first-line option in view of his ischaemic lower leg. In contrast to this, despite poor prognosis following CT angiogram, Patient D achieved successful wound healing and to date has only had one episode of further ulceration, which required surgical debridement. The amputation site subsequently healed and has remained intact since 5 weeks after this debridement.

The prediction of successful healing and appropriate application of the TMA continue to be based on clinical judgement. In a review of 62 TMAs, Landry et al. were unable to identify any accurate preoperative measures that could predict healing [21]. A significant problem with this patient group is that the majority often have comorbidities that can affect wound healing and therefore predispose to postoperative complications. Landry et al. [22] identified that poor glycaemic control (measured by glycated haemoglobin) is a significant risk factor for progressing to a more proximal amputation. In addition to this, particular risk factors such as diabetes mellitus, infrapopliteal disease, and history of smoking and renal disease can certainly be identified prior to the decision on the most appropriate intervention [23]. The determination of the most appropriate level of amputation remains a vexing surgical problem.

Anthony and colleagues [11] recognised the need for the development of selection criteria to identify those patients who are likely to be best served by a TMA as opposed to a higher level of amputation. 56% of the patients in their study required a more proximal amputation; however, most had significant comorbidities with 89% being graded as American Society Anaesthesiology class 3 or 4. The authors note that the only factor significantly related to more proximal amputation was non-insulin-requiring diabetes. We note a similar trend in our cohort of patients. As yet, no definitive selection criteria for patients undergoing TMA exist.

4. Postoperative Considerations

Consideration of domestic circumstances of individual patients, particularly in situations where patients may have reduced mobility, is crucial in ensuring that patients can be safely discharged from hospital. Following discharge, the influence of healthcare providers is significantly reduced and there is a duty to ensure that an adequate social care framework exists. Ensuring these patients remain in hospital for a longer period postoperatively ensures that wounds are stable upon discharge and should therefore be less likely to breakdown as a result of early noncompliance. Input from physiotherapy to improve ambulation with introduction of walking aids or increasing body strength can be utilised within the community or whilst the patient is an inpatient. The acute stay episode may be used by social services and/or the occupational therapist to assess the patient's home and make amendments as necessary. These simple measures can increase compliance and lower readmission and further surgery rates. WMUH statistics have shown that in the year

prior to the implementation of this approach in managing the diabetic foot (2006) 16 BKAs/AKAs were performed. This reduced dramatically with only one BKA/AKA performed in both 2008 and 2009. Undoubtedly, there may be other factors responsible for a reduction in more proximal amputations; however, it is reasonable to infer that this approach can be a contributing factor in such a reduction.

Pressure reducing techniques such as pressure deflecting dressings, foot orthoses, footwear modifications, and total contact casting may be used because they have good effect in reducing pressure around neuropathic foot ulceration to facilitate wound healing. These modalities may also be used postoperatively following TMA. The clinician must use experience and expertise to determine the most appropriate treatment for each patient on an individual basis.

Several authors have suggested that patients who have undergone TMA experience minimal functional deficits and that an observer would have difficulty, when a patient is wearing footwear, in telling that a TMA had been performed [10, 24]. However, in a comparison of the functional ability of TMA patients with age-matched controls, Mueller and colleagues [9] found that TMA patients scored much lower in functional tests (some of which involved simple tasks such as simulating eating and putting on a coat) but higher than those with a higher level of amputation in other studies. An obvious explanation for reduced limited function is the decreased foot length. This results in considerable difficulty when performing activities involving transfer of weight onto the forefoot such as walking at normal speed and climbing stairs. Factors such as obesity, visual limitations, and other comorbidities were not taken into consideration in this study; however, poor scores would indicate that these factors are pertinent. The low scoring provides the reader with an insight as to how poor the general well-being of TMA patients can be.

Diabetic patients with TMA show decreased power at the ankle joint and earlier onset of hip flexor moments and also have limited push-off power therefore relying more on pulling their leg through gait than age-matched controls [25]. Footwear therefore has a role to play in aiding ambulation and improving gait characteristics. As well as enhancing function of the foot, footwear should also protect the residuum and also the contralateral foot from increased loading. An investigation into various footwear modifications for TMA patients showed total contact shoe inserts and rigid rocker bottom soles to both reduce plantar pressures and enhance function. A foot-ankle orthosis and short shoe to match decreased foot length did not enhance functional stability, and these were poorly tolerated by patients [26]. Our patients are routinely referred on an urgent basis to the orthotist within our hospital for the provision of bespoke footwear with a rocker soled shoe and total contact insert.

5. Conclusion

Transmetatarsal amputation is an effective procedure in the treatment of severe forefoot infection/ulceration. Where the forefoot is rendered nonviable, the patient can return to full ambulation and independence providing postoperative complications are avoided or managed appropriately. The TMA does not come without risk, and high failure rates have been well documented throughout the literature. Consideration of the adjunctive soft tissue procedures and mechanical post-operative modalities available is important in providing the greatest chance of avoiding further breakdown. This highlights the need for careful patient selection and also recruitment of the whole multidisciplinary team. The benefit of reduced morbidity and maintenance of function when successful make the procedure preferable to more proximal amputations in our experience.

Conflict of Interests

Neither author has any conflict of interests to declare.

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Research Article

Intermuscular Adipose Tissue Is Muscle Specific and Associated with Poor Functional Performance

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Purpose. People with obesity, diabetes, and peripheral neuropathy have high levels of intermuscular adipose tissue (IMAT) volume which has been inversely related to physical function. We determined if IMAT is muscle specific, if calf IMAT is different between a healthy obese group (HO), a group with diabetes mellitus (D), and a group with diabetes mellitus and peripheral neuropathy (DN), and if IMAT volume or the ratio of IMAT/muscle volume is related to physical function in these groups. *Methods*. 10 healthy obese people, 11 with type 2 diabetes, 24 with diabetes and peripheral neuropathy, had assessments of muscle morphology, physical function and muscle performance. *Results*. The gastrocnemius muscle had a higher ratio of IMAT/muscle volume than any other muscle or compartment. There were no differences between groups in calf muscle or IMAT volumes. Calf IMAT was inversely related to physical performance on the 6-minute walk test ($r = -0.47$) and physical performance test ($r = -0.36$). IMAT/muscle volume was inversely related to physical performance (PPT, $r = -0.44$; 6 MW $r = -0.48$; stair power, $r = -0.30$). *Conclusions*. IMAT accumulation varies in calf muscles, is highest in the gastrocnemius muscle, and is associated with poor physical performance.

1. Introduction

Previous research has shown that people with obesity, diabetes, and peripheral neuropathy have significantly greater amounts of intermuscular adipose tissue (IMAT) in the calf compared to a nonobese control group and that this calf IMAT was associated with poor physical performance [1]. The unique contributions of obesity, diabetes, and diabetes in combination with peripheral neuropathy to the amount of IMAT in skeletal muscle, however, are not clear. In addition, the relationship between calf IMAT and physical performance is not clear in these groups. IMAT is defined as the visible adipose tissue beneath muscle fascia and between muscle groups [2, 3]. IMAT in the thigh has been linked to insulin resistance and has been described as a unique adipose tissue depot that is similar to visceral adipose tissue in its risks for metabolic impairment [4–6], but little is known about IMAT in the calf muscles. Previous investigators [5, 6] have shown that IMAT is linked to insulin resistance and that denervation [7] can also contribute to fat infiltration in muscle, but it is unclear how the combination of obesity, diabetes, and peripheral neuropathy impacts IMAT infiltration.

It is also unknown whether calf IMAT accumulation is muscle or muscle compartment specific, that is, whether one muscle or a group of muscles tends to have more IMAT than others. Identifying preferential differences in IMAT accumulation may help to understand the purpose of IMAT. Muscles in the calf have different distributions of fast twitch and slow twitch fibers. For example, the gastrocnemius muscle is considered predominantly a fast twitch muscle and is used more for large force production, while the soleus muscle is considered more slow twitch and is a postural muscle that is better suited for using lipids as a fuel source [8]. It has been shown in animal models that there is a difference in fatty acid transport in muscles with different fiber type distributions (type I/red muscles are more oxidative than type II/white) and that fatty acid transport and triacylglycerides in muscle are impacted by insulin resistance and diabetes [9]. Additionally, increased triglyceride storage has been shown in the type I fibers of

the soleus in obese rats [10]. It is unknown in humans whether muscles with different "predominance" of fiber types are targeted by IMAT infiltration in the presence of obesity, diabetes, and diabetes combined with neuropathy. A better understanding of IMAT distribution within the calf will provide us with insight into muscles that may be more compromised by fatty infiltration and may lead to improved rehabilitation strategies in these populations.

Therefore, the purposes of this study were to determine if IMAT accumulation is muscle specific, that is, determine difference in IMAT volumes between individual muscles and muscle compartments, if calf IMAT is different between groups of healthy obese people (HO), a group with diabetes mellitus (D), and a group with diabetes and peripheral neuropathy (DN), if IMAT and/or the ratio of IMAT/muscle volume is related to function in these groups. We hypothesized that the soleus muscle would display more IMAT than the gastrocnemius muscle and all other calf compartments across the three groups due to the predominance of slow twitch fibers and higher lipid oxidation capacity in the soleus muscle. Additionally, we hypothesized that the D and DN groups would have greater volumes of IMAT in the calf, and similar calf muscle volumes compared to the HO group, and that the DN group would display the largest volume of calf IMAT of all 3 groups. We hypothesized that calf IMAT volume would be inversely correlated with measures of physical performance.

2. Methods and Procedures

2.1. Participants. Forty-five subjects participated in this study (Table 1). The groups were matched for age and BMI. Initially, there was an analysis of a group of 10 DN subjects who best matched the 10 individuals in the other 2 groups. However, this did not change the results and increased the DN group variability. This led to reporting the larger group of DN subjects.

Participants were recruited from the Washington University School of Medicine Diabetes Clinic, Washington University's Volunteers for Health, the Center for Community Based Research, and from diabetes clinics in the surrounding St. Louis community. This study is part of a larger study investigating the effect of exercise for people with diabetes and peripheral neuropathy. Participant characteristics are listed in Table 1. Participants were excluded if they weighed more than 300 pounds (equipment weight limit) or had a history of severe foot deformity or amputation, any comorbidity or medications that would interfere with exercise (such as severe rheumatoid arthritis, peripheral arterial disease (absent pulses), dialysis, or current cancer treatment). Participants provided written informed consent. This study was approved by the Human Research Protection Office at Washington University in St. Louis.

3. Assessments

3.1. Peripheral Neuropathy. Presence of peripheral neuropathy was determined based on both an inability to feel the 5.07 Semmes-Weinstein monofilament on at least one point on the plantar surface of the foot and on a vibration perception threshold greater than 25 V as measured with a biothesiometer applied to the plantar surface of the great toe [11, 12]. All subjects were tested for presence of neuropathy; to be included in the D and HO groups, subjects had to be able to feel the 5.07 monofilament and have a vibration perception threshold below 25 V.

3.2. Intermuscular Adipose Tissue (IMAT). Calf intermuscular adipose tissue volumes were quantified using MRI on the right leg of each participant. The MRI scans were performed with the participant in a supine position with a Siemens CP extremity coil placed over the right calf muscle. The MRI measurements were performed with a 3.0 Tessla superconducting magnet with a pulse sequence of TE = 12 milliseconds, TR = 1,500 milliseconds, matrix = 256×256; both a fat-saturated and a non-fat-saturated image were collected [1]. Thirty transverse slices were collected beginning at the joint space of the knee and proceeding distally. The slices were 7 mm thick with no interslice gap. Nine consecutive slices were selected to calculate muscle and IMAT volumes. Volumes were quantified using a PC workstation and custom Matlab software. The software uses voxel brightness to distinguish between muscle and adipose tissues [6, 13, 14]. The subcutaneous adipose tissue was removed from each image by drawing a line along the deep fascial plane surrounding the calf muscle so that only the fat within and between the muscles (IMAT) was remaining. The software uses edge detection algorithms to assist the user in separating the subcutaneous fat from the muscle as well as separating individual muscles and muscle compartments. In the calf, the muscle was divided into (1) the anterior compartment, (2) the lateral compartment, (3) the deep compartment, (4) the gastrocnemius muscle, and (5) the soleus muscle (Figure 1). Calf IMAT and calf muscle volumes are reported in cm^3. An additional variable, IMAT per muscle volume, was also used in analysis. Based on test-retest reliability of 21 subjects (group included people who are obese, people with diabetes, and people with diabetes and peripheral neuropathy), the error in measuring muscle volume is less than 1% and less than 2% for measuring fat volumes on average in any muscle or compartment [15].

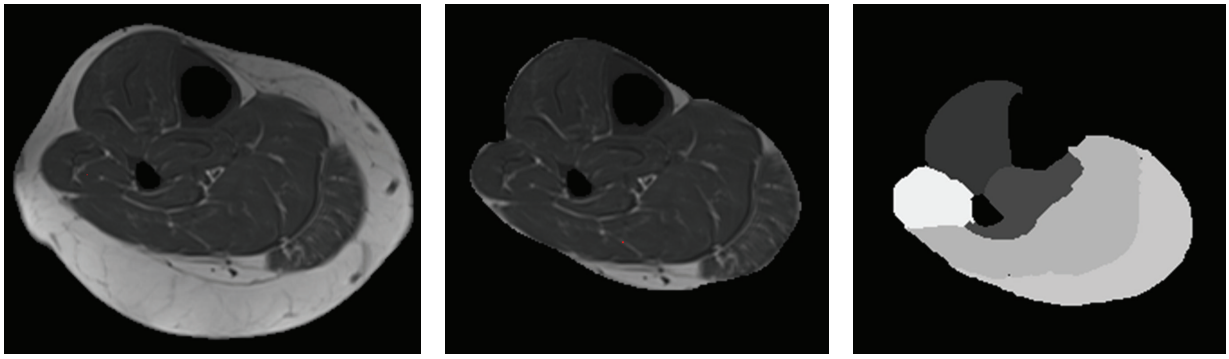
3.3. Six-Minute Walk Test. All participants performed the six-minute walk test [16] which was validated previously in obese adults [17]. The participants walked back and forth in a hallway between 2 cones that were placed 100 feet (30.5 m) apart. The participants were instructed that the goal was to walk as far as possible in 6 minutes. Six-minute walk distance was recorded as total distance walked (in meters).

3.4. Physical Performance Test (PPT). The modified 9-item PPT was used to assess physical performance in all participants. This test is designed to mimic activities of daily living, and the 9-item PPT has been shown to correlate well with disability and frailty [18–20]. The 9-item PPT includes placing a book on a shelf, putting a lab coat on and taking it off, picking up a coin from the floor, a 25-foot walk down and back at a fast speed, turning in a 360-degree circle, simulated

Table 1: Subject demographics by group. Values are means (SD).

Group	N	Gender (M/F)	Age (years)	BMI (kg/m^2)	Weight (lbs)	Diabetes medication (oral only/insulin and oral)	HbA1c (%)	DM duration (years)
HO	10	4/6	64 (9)	32.9 (4.6)	213 (41)	NA	5.8 (0.2)	NA
D	11	5/6	56 (9)	35.5 (6.4)	226 (33)	6/5	8.1 (2.2)	8.1 (6.9)
DN	24	15/9	64 (13)	32.6 (6.3)	217 (45)	13/11	7.1 (1.3)	12.9 (9.0)

NA: not applicable.



(a) (b) (c)

Figure 1: (a) MRI image of calf with bone removed. (b) Subcutaneous adipose tissue removed. (c) Calf divided into 5 compartments (anterior, lateral, deep, gastrocnemius, and soleus).

eating, writing a sentence, climbing a flight of stairs with 10 steps, and sitting to standing 5 times from a low chair. Each of the items is scored on a scale of 0–4 based on the time it takes to complete the task. Each task is performed twice, and the average time is used to determine the 0–4 score. A maximum score is indicated by a score of 36.

3.5. Stair Power Measure. Stair power (in watts) was calculated based on the time it took each participant to climb a flight of 10 stairs as part of the PPT (average of 2 trials) using the following formula which was adapted from the stair sprinting power test [21]:

$$\begin{aligned}
\text{Stair Power} &= 3.171 \ * \ \text{Weight (kg)/time (sec)} \\
&\quad \text{Climb avg} \ * \ \frac{1}{.1383} \ * \ \frac{1}{.7378}, \\
\text{where } 3.171 &= \ \text{distance traveled (m)}, \\
\text{Climb avg} &= \text{average time to} \\
&\quad \text{climb a flight of 10 stairs (sec)}, \\
\frac{1}{.1383} &= \text{conversion} \left(\frac{\text{kgm}}{\text{s}} \ \text{to} \ \frac{\text{ftlbs}}{\text{s}} \right), \\
\frac{1}{.7378} &= \text{conversion} \left(\frac{\text{ftlbs}}{\text{s}} \ \text{to Watts} \right).
\end{aligned} \tag{1}$$

Subjects were allowed to touch a handrail for balance, but not for pulling or pushing to ascend the stairs.

3.6. Ankle Dorsiflexion and Plantarflexion Peak Torque and Power. Concentric isokinetic ankle dorsiflexor and plantarflexor peak torque and power were assessed using a Biodex Multijoint System 3 Pro isokinetic dynamometer. The tests were performed at angular velocities of 60°/s. The average power at 60°/s was determined by the time-averaged integrated area under the curve at the constant velocity of movement in the available range of motion [1]. All participants were given 3 practice trials to ensure they were comfortable with the test. The mean values for peak torque and average power were calculated for 3 trials.

3.7. Statistical Methods. Statistical analyses were performed using Systat for windows, version 13.0. An analysis of variance was used to examine the main and interaction effects of calf IMAT and muscle volumes (gastrocnemius, soleus, anterior compartment, lateral compartment, and deep compartment), group (HO, D, DN), and measures of physical performance. Post hoc t-tests were used to examine differences in groups (HO, D, and DN) on the variables of calf IMAT volume, calf muscle volumes, and physical performance as needed based on the results of the ANOVA. A Pearson correlation was used to examine the associations between variables across all 45 subjects—all scatter plots were inspected and analyzed for outliers. Significance level was set at $P = 0.05$.

4. Results

There were no group differences in age, BMI, or weight ($P > 0.05$). The HO group was significantly different from the other groups in HbA1c and DM duration—the D and

Table 2: ANOVA results: muscle morphology measures; all values are means (SD) in cm^3.

	HO	D	DN	*P* values
Muscle volume	404 (90)	434 (72)	407 (88)	0.65
IMAT volume	67 (54)	65 (36)	70 (40)	0.94
Anterior compartment muscle volume	62 (9)	69 (15)	65 (14)	0.57
Anterior compartment IMAT volume	7 (5)	10 (11)	9 (5)	0.53
Lateral compartment muscle volume	36 (10)	38 (9)	37 (11)	0.85
Lateral compartment IMAT volume	6 (5)	5 (3)	7 (4)	0.62
Deep compartment muscle volume	51 (15)	54 (13)	60 (12)	0.15
Deep compartment IMAT volume	9 (6)	8 (4)	11 (5)	0.23
Soleus muscle volume	127 (28)	130 (26)	118 (32)	0.46
Soleus IMAT volume	14 (14)	14 (8)	15 (10)	0.97
Gastroc. muscle volume	128 (31)	142 (27)	122 (40)	0.35
Gastroc. IMAT volume	31 (28)	27 (15)	28 (21)	0.90
IMAT/muscle volume	0.144 (0.07)	0.158 (0.11)	0.193 (0.16)	0.58

Anterior compartment: comprised of tibialis anterior, extensor digitorum longus, and extensor hallucis longus muscles.
Lateral compartment: comprised of peroneus longus and brevis muscles.
Deep compartment: comprised of the tibialis posterior, flexor digitorum longus, and flexor hallucis longus muscles.

Table 3: ANOVA results: physical performance measures. Values are means (SD).

	HO	D	DN	*P* values
DFPT (Nm)	5.2 (4.3)	15.3 (7.5)[a]	4.5 (5.3)	0.00
DFPOW (W)	2.3 (2.4)	9.8 (6.6)[a]	2.2 (3.2)	0.00
PFPT (Nm)	58.0 (18.6)	48.1 (13.0)	51.4 (16.5)	0.37
PFPOW (W)	45.9 (15.1)	38.7 (10.9)	41.9 (18.1)	0.38
6 MW (m)	512.4 (48)[a]	459.6 (80)	425.5 (98)	0.04
PPT	34 (1.5)	31 (2.4)	28 (4.0)	0.001*
Stair power (W)	808 (327)	671 (163)	601 (226)	0.04*

* Indicates all 3 groups are different.
[a]Indicates that the group is different from the other 2 groups.
DFPT: dorsiflexor peak torque; DFPOW: dorsiflexor power; PFPT: plantarflexor peak torque; PFPOW: plantarflexor power; 6 MW: six-minute walk distance; PPT: physical performance test (9 items).

DN groups were not significantly different on these measures. The gastrocnemius muscle had a higher ratio of IMAT/muscle volume than any other muscle or compartment ($P = .005$) across all participants (Table 2).

There were no group differences between any of the calf muscle or IMAT volume measures (Table 2). Group differences were determined for descriptive purposes and are contained in Table 3.

Across all participants, calf IMAT volume was associated with BMI ($r = 0.31$) and IMAT volume was associated with poorer physical performance on the 6-minute walk test ($r = -0.47$) and the physical performance test ($r = -0.36$). IMAT/muscle volume was also associated with poor physical performance (PPT $r = -0.44$, 6 MW $r = -0.48$). Muscle volume was not strongly associated with 6-minute walk distance or physical performance test score but was associated with stair power ($r = 0.51$) (Table 4).

5. Discussion

This study is the first to report that the amount of IMAT/muscle volume in the calf is muscle and compartment specific in the pathologies of obesity, diabetes, and diabetes combined with peripheral neuropathy. The gastrocnemius muscle had the largest ratio of IMAT/muscle volume compared to any of the calf muscles and compartments, which was contrary to what we expected and to what has been reported in obese animal models [9, 10]. We speculate that perhaps those muscles with a predominance of fast-twitch fibers, such as the gastrocnemius muscle, are affected by IMAT accumulation preferentially or sequentially. The plantar flexor muscles are important for ankle stability, walking velocity, and cadence [22]. Furthermore, the gastrocnemius is used during powerful and phasic/burst type activity compared to the soleus muscle which is most active for postural control. Perhaps the gastrocnemius is more affected by IMAT than the soleus muscle due to a greater reduction in power activities compared to postural activities in these groups. Or, perhaps the reduced lipid metabolism in the gastrocnemius muscle compared to the soleus muscle results in greater IMAT storage rather than lipid oxidation. Additional studies are required to determine the underlying mechanisms for the IMAT accumulation in the gastrocnemius muscle and its propensity for having greater fat infiltration than other calf muscles. Understanding the muscle specific distribution of fat and the underlying mechanisms for fat infiltration may lead to enhanced treatment strategies to improve the health of the muscle and individual. For example, Marcus et al. [23] demonstrated that people with type 2 diabetes were able to improve performance, decrease fat, and increase lean tissue in the thigh muscles after a 16-week exercise program that included both aerobic and high-intensity eccentric exercise training. Perhaps specific rehabilitation strategies that target the gastrocnemius muscle could alter the fat infiltration and

Table 4: Correlation matrix.

	IMAT vol	6 MW	PPT	Stair POW	Muscle Vol	IMAT/Mus Vol
BMI	0.31*	−0.18	0.01	0.21	0.49*	0.08
IMAT vol		−0.47*	−0.36*	−0.18	−0.32*	0.93*
6 MW			0.79*	0.58*	0.25	−0.48*
PPT				0.60*	0.24	−0.44*
Stair Pow					0.51*	−0.30*
Muscle vol						−0.35*

*Indicates significance ($P < 0.05$).
IMAT: intermuscular adipose tissue volume; 6 MW: six-minute walk distance; PPT: physical performance test (9 items); Stair Pow: stair power; Muscle Vol: calf muscle volume; IMAT/MusVol: ratio of IMAT/muscle volume in the calf.

improve deficits in muscle performance and physical performance.

Overall, the inverse correlation between calf IMAT volume and physical performance indicates that IMAT accumulation is associated with physical performance decline, but it appears that there are other factors, such as the presence of diabetes and/or neuropathy, that are key mediators of physical performance. The ratio of IMAT/muscle volume was inversely related to measures of muscle performance across all subjects. The ratio of calf IMAT/muscle volume may be an indicator of physical performance, but the IMAT/Muscle volume does not differ between those with diabetes and diabetes and neuropathy compared to a healthy obese group of subjects. These results are consistent with other reports in the literature and suggest measures other than absolute muscle volume or muscle cross-sectional area are needed to completely characterize calf muscle composition and muscle performance [1, 24] and suggest that perhaps IMAT/muscle volume may be an indicator of "muscle quality." These data are also consistent with reports that people with D or DN have limitations in physical performance and function beyond what is fully explained by muscle changes alone [24, 25]. Certainly problems secondary to sensory neuropathy can contribute to these deficits in physical performance [26].

We found, contrary to our expectations, that there were no group differences in measures of IMAT volumes or muscle volumes between a group with HO, a group with D, and a group with DN. These results indicate that diabetes and peripheral neuropathy were not associated with IMAT accumulation in the calf beyond their association with BMI in these groups of subjects. These results were surprising because our previous study indicated that a group with obesity, diabetes, and peripheral neuropathy had two times the volume of IMAT compared to a nonobese, nondiabetic, nonneuropathic control group [1]. Four of the six subjects with DN in that group were sampled from a patient sample with a history of foot ulcers rather than the community at large, so it is likely that we were capturing a group with more severe neuropathy in the previous study compared to what we report here.

Of note, the HO group had an average HbA1c value of 5.8 which is indicative of people at risk for developing diabetes [27]. This HbA1c value is consistent with other reports in the literature that link IMAT with insulin resistance [5, 6], and this marginally high HbA1c value could be a potential indicator of those at risk for developing diabetes. Interestingly, the HO group had higher levels of physical performance than the D or DN groups, so perhaps an intervention targeted at minimizing IMAT could diminish risk for developing diabetes and mitigate the functional decline that is associated with diabetes and diabetes and peripheral neuropathy.

There are limitations that should be considered. First, we have a relatively small sample size. Based on the small effect size between groups, a post hoc power analysis revealed that we would need to collect data on more than 3600 individuals to be powered to find group differences in total IMAT in the calf with a power of 0.80 and an alpha level at 0.05. The magnitude and impact of IMAT accumulation in specific calf muscles or compartments in people with severe diabetes and peripheral neuropathy requires additional investigation. We are limited in our ability to interpret results because we do not have biopsies or other biochemical measures of the individual muscles or adipose tissues to further elucidate characteristics beyond our macroscopic MRI measures. This study is also limited in that we do not have a measure of activity level for each participant, so it is possible that our groups could be different from each other in levels of activity. Future studies should characterize subjects on activity level, activity types (endurance versus strengthening exercise), and neuropathy severity to enhance interpretation of results. We do not have electrodiagnostic measures of neuropathy, and it possible that electrodiagnostic measures would have provided us with a more accurate measure of neuropathy severity including a measure of subclinical neuropathy in the D or HO groups. Since the group with DN was originally recruited for an exercise study, it is possible that we have a selection bias towards people with DN who are higher functioning. In addition, this group only had 2 people with a history of plantar foot ulcer, so we do not believe these results are generalizable to people with more severe complications and longer durations of diabetes and peripheral neuropathy. Lastly, the correlations between the different variables only indicate association and cannot determine cause and effect.

In conclusion, this study found that increased calf IMAT volume accumulation was muscle specific; the gastrocnemius muscle had the largest ratio of IMAT/muscle volume of all of the calf muscles and compartments. In addition, calf

IMAT was associated with poorer physical performance. The groups with D and DN had lower measures of physical performance than the HO group, suggesting that more severe impairment in metabolic pathology, along with IMAT accumulation, impacts physical performance.

Conflict of Interests

The authors deny any conflict of interests present in this work.

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