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Early-onset physical frailty in adults with diabesity and peripheral neuropathy

Lori J. Tuttle, PT, PhD[a], **Daniel C. Bittel, PT, DPT**[b], **Adam J. Bittel, PT, DPT**[b], and **David R. Sinacore, PT, PhD, FAPTA**[b]

[a]Doctor of Physical Therapy Program, San Diego State University, San Diego, CA, 5500 Campanile Drive., Mail Code 7251, San Diego, CA 92182, USA

[b]Program in Physical Therapy, Washington University School of Medicine, St Louis, MO, 4444 Forest Park Ave., Campus Box 8502, St. Louis, MO 63108, USA

Abstract

Objective—Diabesity (obesity and diabetes mellitus) has been identified as a potential contributor to early onset frailty. Impairments contributing to early onset of physical frailty in this population are not well understood and there is little evidence of the impact of peripheral neuropathy on frailty. The purpose of this study was to determine impairments that contribute to early-onset physical frailty in individuals with diabesity and peripheral neuropathy.

Patients and Methods—One hundred-five participants were studied: 82 with diabesity and peripheral neuropathy (57 years old, BMI 31 kg/m^2), 13 with diabesity only (53 years old, BMI 34 kg/m^2), and 10 obese controls (67 years old, BMI 32 kg/m^2). Peripheral neuropathy was determined using Semmes Weinstein monofilaments, physical frailty was classified using the 9-item, modified Physical Performance Test, and knee extension and ankle plantarflexion peak torques were measured using isokinetic dynamometry.

Results—Participants with diabesity and peripheral neuropathy were 7.4 times more likely to be classified as physically frail. Impairments in lower extremity function were associated with classification of frailty.

Conclusions—Individuals with diabesity and peripheral neuropathy are particularly likely to be classified as frail. Earlier identification and interventions aimed at improving lower extremity function may be important to mitigate the early-onset functional decline.

Keywords

Diabetes; Obesity; Frailty

Corresponding Author: Lori Tuttle, Doctor of Physical Therapy Program, San Diego State University, 5500 Campanile Drive., Mail Code 7251, San Diego, CA 92182, Tel: 619-594-1918, Fax: 619-594-6553, ltuttle@mail.sdsu.edu.

Introduction

Frailty can be described as a clinical state of aging-associated decline in function and functional reserve and is a combination of slowness, weakness, exhaustion and low activity that can impair the performance of fundamental functional tasks [1]. Consequences of frailty include disability, hospitalization, fragility fracture, institutionalization, and early mortality [2,3]. Comorbidities including diabetes have been associated with frailty and increased risk for frailty [4,5]. The specific phenotype of type 2 diabetes mellitus (T2DM) that develops with aging and is associated with obesity has been termed diabesity [6].

Historically, frailty has been investigated and defined in older adults (>65 years of age) with the prevalence increasing with advancing age [7]. The use of an age range of 65 years and older does not account for frailty that can occur at an accelerated rate, for example in individuals with diabesity and individuals with diabesity and peripheral neuropathy. It has been noted that the comorbidity of diabetes confers an accelerated aging process [8], and increased risk of frailty [5], yet there has been limited study into the impairments and limitations that may be related to frailty in this younger population. Additionally, there is little information about how the presence of peripheral neuropathy may impact frailty in the diabese population. Data from the Centers for Disease Control indicate that 60% of people with diabetes who are 45–60 years of age report mobility limitations in simple tasks including walking a quarter mile, climbing 10 steps, standing for 2 hours, and stooping, bending or kneeling [9]. It is important for primary care physicians, geriatricians, neurologists, endocrinologists, and rehabilitation specialists to understand impairments and screening tools that may identify people who are frail or at risk for frailty so targeted interventions may be initiated at the earliest possible time.

There are a variety of screening tools used to determine the presence of frailty in older adults and the elderly including walking speed [10], grip strength [10], and the modified Physical Performance Test (mPPT) [11,12]. While walking speed and grip strength may contribute to frailty, they do not include many common ADLs that were reported as limited in the CDC report such as stair climbing and bending or kneeling. The Physical Performance Test upon which the mPPT is based, provides a more global assessment of physical function and has been correlated with disability, institutionalization, and mortality [13,14]. This more global assessment of function, including tasks that are more physically demanding, may be an important screening tool and indicator of frailty in a younger patient population and warrants investigation.

It is critical that we have a better understanding of impairments that contribute to early-onset physical frailty in patients with diabesity, particularly of impairments that may be modifiable such as muscle performance of the lower extremity. Given previous evidence of early-onset frailty in individuals with diabesity, or both diabesity and peripheral neuropathy, it is especially important to understand how these impairments increase the risk for frailty in this population. Therefore, the purpose of this study was to determine the impact of peripheral neuropathy on physical frailty and to determine measures of lower extremity function that are associated with frailty classification. We hypothesized that stair climbing and rising from

a chair would be measures of lower extremity function that would be associated with frailty classification due to their increased demand on the lower extremities.

Methods

Participants

One hundred-five participants were studied: 82 with diabesity and peripheral neuropathy (DMPN), 13 with diabesity only (DM), and 10 obese controls without diabetes (CON). The main focus of our analysis was on the 82 participants with DMPN, however we included participants with DM only and obese controls without DM to determine the impact of PN and DM on frailty. Participants were recruited from the Washington University School of Medicine Diabetes Clinic, Washington University's Volunteers forHealth, the Center for Community Based Research, and from the surrounding St. Louis Community. Study inclusion criteria included individuals with body mass index (BMI) greater than 27 kg/m^2, with or without a diagnosis of diabetes mellitus and with or without evidence of peripheral neuropathy. DM status was based on subject report of a diagnosis of DM from a physician, confirmation of medication usage for DM (insulin, oral hypoglycemic agents or both) and verification of HbA1c levels. Participants were excluded from the study if they weighed more than 300 pounds (equipment weight limit), presented with any illness or hospitalization within the last 6 months, had any infection or ulceration on either foot, had prior botulinum toxin injections, severe foot deformity or amputation, or any co-morbidity or medication that would limit participation in physical activity testing. All participants signed their informed consent based on protocol that was approved by the Human Research Protection Office's institutional review board at Washington University School of Medicine in St. Louis, MO.

All testing took place in a single testing session. Examiners were not blinded to group assignment (DM, DMPN, CON).

Neuropathy Assessment

Presence of peripheral neuropathy was based on an inability to sense the 5.07 Semmes-Weinstein monofilament on at least 1 of 7 non-callused areas on the plantar surface of the foot (great toe, metatarsal heads 1–5, heel) [15,16,17].

Modified Physical Performance Test

The modified 9-item Physical Performance Test (mPPT) was used to assess physical function and determine classification of physical frailty. The mPPT is based on the Physical Performance Test originally described by Reuben and colleagues [13,14]. The mPPT replaces writing a sentence and simulated eating with a chair rise task and standing balance task, which are correlated with nursing home placement and loss of independence [18]. The 9-item mPPT mimics activities of daily living and correlates well with disability and frailty [11, 19, 20, 21, 22, 23]. Each item is scored from 0–4 based on the time (in sec) to complete each task. Each task is performed twice with the average time used to score the task. A maximum score is 36 points and a score of <29 points indicates moderate physical frailty as scores of less than 30 are functionally below the 75^{th} percentile of community dwelling

older adults [13]. DMPN were stratified into frailty classifications based on mPPT score: mild to no frailty (mPPT=30–36), moderate frailty (mPPT=22–29), severe frailty (mPPT=21 or less). This is consistent with the work by Reuben and colleagues using the original PPT [13] that a score of 29 or less indicates a level of function below the 75th percentile of community dwelling adults and a score of 21 or less indicates function below the 25th percentile of community dwelling adults. Interrater reliability, validity with other functional assessments, and predictive validity of lack of independence and mortality have been reported previously for both the PPT and mPPT [11,13,14, 24]. The mPPT has been reported to have a test-retest reliability of .964 and individual items have reliability of .51–.99 and a Cronbach alpha of .785 [24, 25]. Tasks include lifting a book to an overhead shelf, donning and doffing a lab coat, picking up a coin from the floor, walking 50 feet, climbing one flight of stairs, climbing four flights of stairs, performing 5 sit to stand transfers from a 16 inch chair height, turning 360 degrees while standing, and standing balance (tested in side by side, semi-tandem, and tandem standing as tolerated). Stair power was calculated from the time it took to climb one flight of stairs using a previously reported method [26].

$$Power = \frac{mass \times (-9.8 m/s^2) \times Height\ 10\ Steps}{Time\ to\ C\ \lim\ b\ Steps\ (\ \sec\ )}$$

Muscle Performance: Knee Extension and Ankle Plantarflexion Peak Torque

Knee extension and ankle plantarflexion peak torque were measured using a Biodex Multijoint System 3 isokinetic dynamometer at 60 degrees/second on the right leg. All participants were give 3 practice trials to ensure they were comfortable with the testing procedures. The mean values for average peak torque in Nm were calculated for 3 trials.

Data Analyses

Chi-square analysis was used for equality of proportions for sex distribution, and group differences in frequency of frailty classifications. To examine the impact of peripheral neuropathy on frailty, Fisher's Exact test was utilized to determine the odds of frailty classification (severe, moderate, mild to no frailty) between those with peripheral neuropathy and those without peripheral neuropathy. Group differences in demographics between diabese and control groups were analyzed using 1-way ANOVAs, while group differences in mPPT score (used to classify frailty) were determined with 1-way ANCOVA to control for gender, age, duration of DM, and HbA1c (glycemic control). Group differences among the severe frail, moderate frail and mild to non-frail groups for mPPT scores, individual items on the mPPT and peak torque measures were also analyzed using 1-way ANOVAs. Post hoc testing for individual group differences was determined using Tukey's HSD or Games-Howell as appropriate. Bivariate Pearson Correlation Coefficients were used to assess inter-relationships between contributor measures. An alpha value of 0.05 indicated significant findings.

Results

In our sample, 61% of the DMPN group was frail, 30% of the DM group was frail, but none of the CON participants were frail (Table 1). There was a significant difference in mPPT score between disease groups, with DMPN having the lowest score (mean 25.8), followed by the DM group (mean 30.5), and the obese CON group had the highest mPPT score (mean 34.2). Scores on mPPT were significantly different between these groups, even after controlling for age, gender, duration of diabetes, and HbA1c. Moreover, participants with diabesity and peripheral neuropathy were 7.4 times more likely to be classified as physically frail than those without DMPN (X^2=15.8, p<0.001). The Fisher's Exact test was significant (p=.04) indicating that participants were more likely to be classified as severely frail or moderately frail if they had peripheral neuropathy.

Based on these data and the larger sample size of our DMPN group, we focused our subsequent analysis of impairments on the DMPN group. Based on our analysis of individual items of the mPPT in the DMPN group, the chair rise test and 50 foot walk test were significantly different between the severe frail, moderately frail, and the mild to no frail groups. There was also a significant difference in vertical stair power, knee extension peak torque, and ankle plantarflexion torque between these groups (Table 2). There were significant differences in the book lift, coin pick up, and don/doff coat tasks and balance tasks. Importantly, there was no difference between the frailty groups in glycemic control (HbA1c, p=0.43) or in duration of diabetes (p=0.30).

Chair rise, stair vertical power, knee extension peak torque, and ankle plantarflexion torque were all significantly correlated with overall mPPT score in the participants with DMPN (Table 3). Additionally, all upper extremity and lower extremity tasks were significantly correlated with overall mPPT score (Table 4), with lower extremity and balance tasks having the highest correlations with mPPT score.

Discussion

To our knowledge, this is the first study to document that the presence of peripheral neuropathy in diabesity dramatically increases the likelihood of being moderately or severely frail in people younger than 65 years of age. Based on our data, the group with diabesity and PN was 7.4 times more likely to be physically frail than those without PN, and this was in a group with an average age of 57 years. Our results show that PN increases the frequency of frailty in people with DM and that lower extremity impairments are associated with the severity of physical frailty. Our hypothesis was supported in that both the chair rise task and the stair climbing task were associated with frailty classification. Additionally, upper extremity tasks were able to discriminate frailty classification in our DMPN group, but the lower extremity tasks (chair rise, stair climb) may be particularly important in these younger patients (<65 years old) as these tasks demand and stress lower extremity strength, which is a known deficit in those with DMPN. The high correlation between lower extremity and balance tasks with overall mPPT score may indicate the particular importance in testing lower extremity function in younger patients with DMPN. Future work is needed in this area to determine the best upper extremity and lower extremity tests for frailty in this population.

The PPT has been used to predict disability, loss of independence and death [13,14], making it a reasonable test to use for frailty classification in this study. The original description of the PPT by Reuben et al. [13] included subjects with an average age of 79 years. Our cutoff score for frailty classification was consistent with a score that indicates a subject was functioning below the 75th percentile of community-dwelling older adults. It is important to note that the participants in this study are significantly younger than those initially described in Reuben's work and significantly younger than many of the studies conducted in frail populations. The average mPPT scores in this study indicate that our subjects with DMPN are functioning at levels between the 25th and 75th percentile for adults that are on average 20 years older than they are (average PPT score 25.9 vs. 21 for 25th percentile and 29 for 75th percentile), average age of 57 years versus 79 years [13]. It is also important to note that lower extremity functional tasks were indicative of severity of frailty in our DMPN group—this included 50 foot walk speed and chair rise score. Stair climbing, stair vertical power and measures of lower extremity muscle function were able to indicate those with severe frailty. All of the items of the mPPT (upper extremity tasks as well as lower extremity tasks) were indicative of frailty classification in our DMPN group. This may indicate that in this younger population, testing that goes beyond self report and includes tasks that are rigorous or functionally **taxing** may be necessary to identify those at risk for frailty. For instance, while the 50 foot walk test was indicative of frailty, the demands placed on the musculoskeletal system to rise from a chair, as in this study, are more than double the requirements for walking [27].

It may be important to begin screening for frailty at an earlier age than what is currently in practice, particularly in the case of those with diabetes and other comorbidities such as PN. The data from the CDC [9] indicating that 40–60 year olds with diabetes report functional difficulty with relatively basic ADLs, including stair climbing, would support this need for earlier screening. In fact, there is evidence that self- report underestimates frailty and dysfunction, so an objective measure like the mPPT may be preferable for early screening in individuals with diabesity [28, 29].

The incidence of frailty in the general population aged 65–70 is 3–6%, and increases to 16% in those 80 years and older [30]. The prevalence of frailty in older subjects with diabetes has been reported to be 32–48% [31,32,33,34,35]. In our sample, the prevalence of frailty in the DM and DMPN groups, was 30% and 61% respectively, despite a mean age of only 53 ± 9 years and 57 ± 12 years. In contrast, none of the obese controls studied were frail (mean age of 67 ± 7 years). This suggests that individuals with DM and particularly those with PN may benefit from advanced screening for frailty and intervention to prevent the further risks of disability and death that are associated with a state of frailty.

There have been several review articles describing diabetes and premature aging, impact on frailty, and targeted interventions for those who are frail [8,36,37]. However, despite the accepted relationship between diabetes and premature aging, these studies still focus on frailty and screening for older adults in their 70s [38,39]. The results of this study as well as CDC data, indicate screening and intervention may need to occur earlier (i.e. 40–60 years of age) in patients with diabetes and neuropathy.

Strengths of this study include use of the mPPT as a descriptor of frailty as it incorporates activities of daily living that include lower extremity function which is often more impaired, particularly in people with DMPN, as well as more functional upper extremity tasks than the more typical use of grip strength as a measure of frailty [10,38]. Limitations include small sample sizes of individuals with DM only and obese controls, which did not allow us to investigate mPPT measures in these other two groups. Future studies with larger samples sizes are warranted. Presence of neuropathy was based solely on monofilament testing rather than using a combination of subjective complaints and other physiological testing. While monofilament testing is a practical and well-established tool for identifying sensory neuropathy [17], we did not use additional testing methods to identify other neuropathy types (i.e. painful neuropathy).

Despite these limitations, this study provides evidence that diabesity, and particularly neuropathy contribute to early onset frailty. Most study has been given to older populations who are frail and/or sarcopenic, despite evidence for people with diabesity having accelerated aging. It is possible that rehabilitation specialists will be the appropriate practitioners to identify these patients and potentially intervene. Further study is warranted to determine if early interventions such as improving lower extremity strength and power can reverse or delay frailty in this younger population of people with diabesity.

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Key Messages

Diabesity (obesity and diabetes mellitus) has been identified as a potential contributor to early onset frailty. Peripheral neuropathy in diabesity increased the likelihood of being moderately or severely frail in people younger than 65 years of age. The group with diabesity and peripheral neuropathy was 7.4 times more likely to be physically frail than those without neuropathy.

Table 1

Participant Demographics by Group

	DMPN	DM	Control	p
Sample Size	82	13	10	---
Age- years	57 (12)	53 (9)	67 (7)	.02 *†‡
BMI- kg/m^2	31 (5)	34 (6)	32 (5)	.30
Gender F, M	27,55	7,6	5,5	.15
Diabetes Mellitus Duration- years	16 (11)	9 (7)	NA	.053
HbA1c (%)	7.9 (1.7)	8.6 (2.1)	5.8 (0.2)	.00 †‡
Able to Sense 5.07 S-W monofilament-%	0	100	100	---
mPPT score	25.8 (7.1)	30.5 (3.4)	34.2 (1.2)	<.001 Δ†^‡
% who are frail	61% (50/82)	30% (4/13)	0% (0/10)	<.001 #†^‡

Data are mean & (SD) or percent & (SD)

* Denotes significant F-test (1-way ANOVA)

# Denotes significant Pearson Chi-Square

Δ Denotes significant 1-way ANCOVA controlling for age, duration of DM, HbA1c, gender

† Denotes significant difference DM vs Control

‡ Denotes significant difference DMPN vs Control

^ Denotes significant difference DM vs DMPN

Table 2

mPPT items analyzed by frailty classification (severe frailty, moderate frailty and mild to no frailty) in DMPN group

	Severe Frailty (N=21)	Moderate Frailty (N=29)	Mild to No Frailty (N=32)	p	Post-hoc
mPPT score cutoff	<21	22–29	30–36	---	---
Chair Rise score (0–4)	0.29 (.56)	1.21 (1.01)	2.50 (.98)	.000	†(p=.000) §(p=.000) ^(p = .000)
50 foot walk score (0–4)	1.81 (.93)	3.62 (.62)	3.97 (.18)	.000	†(p=.000) §(p=.000), ^(p = .017)
50 foot walk time (sec)	24.69 (7.3)	14.81 (2.96)	12.55 (2.21)	.000	†(p=.000) §(p=.000) ^(p = .020)
Stair Climb time (sec)	19.31 (11.8)	8.84 (6.9)	6.08 (1.46)	.001	†(p=.003) §(p=.026)
Stair Vertical Power (Watts)	126.00 (114.91)	332.06 (123.63)	392.63 (125.71)	.000	†(p=.000) §(p=.000)
Knee Extension Torque at 60 deg/sec (Nm)	84.14 (34.13)	114.61 (38.76)	131.81 (37.27)	.001	†(p=.000) §(p=.029)
Ankle Plantar Flexion Torque at 60 deg/sec (Nm)	2.78 (3.13)	10.68 (11.55)	12.99(11.10)	.003	†(p=.001) §(p=.010)
Book Lift score (0–4)	2.90 (.77)	3.40 (.56)	3.71 (.46)	.001	†(p=.001) §(p=.006)
Don and Doff Jacket score (0–4)	2.24 (1.09)	3.09 (.80)	3.65 (.48)	.001	†(p=.001) §(p=.001) ^(p = .003)
Pick Coin up off Floor Score (0–4)	1.67 (1.23)	2.63 (.74)	3.29 (.54)	.001	†(p=.001) §(p=.001) ^(p = .001)
Standing Balance score (0–4)	1.76 (1.22)	3.30 (.81)	3.71 (.54)	.001	†(p=.001) §(p=.001)

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	Severe Frailty (N=21)	Moderate Frailty (N=29)	Mild to No Frailty (N=32)	p	Post-hoc
360 turn score (0–4)	1.43 (1.57)	3.27 (1.10)	3.94 (.42)	.001	†(p=.001) §(p=.001) ^(p = .007)
Stair Climb Score (0–4)	1.33 (1.11)	2.72 (.57)	3.53 (.50)	.001	†(p=.001) §(p=.001) ^(p = .001)

†Denotes significant difference between Severe and Mild Frailty

§Denotes significant difference between Severe and Moderate Frailty

^Denotes significant difference between Moderate and Mild Frailty

Table 3

Correlation Coefficients in DMPN group (N=82) for selected items

	mPPT Score	Right Knee Extension at 60 deg/sec	Right Ankle Plantar Flexion at 60 deg/sec	Chair Rise	Stair Vertical Power
mPPT Score	1	.497**	.439**	−.677**	.696**
Right Knee Extension at 60 deg/sec	.497**	1	.173	−.348**	.643**
Right Ankle Plantar Flexion at 60 deg/sec	.439**	.173	1	−.459**	.377**
Chair Rise	−.677**	−.348**	−.459**	1	−.345**
Stair Vertical Power	.696**	643**	.377**	−.345**	1

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Table 4

Correlation Coefficients for all mPPT items in combined group (N=105)

	Book lift	Jacket	Coin	50 ft walk	360 turn	Standing balance	Chair rise	Stair climb (1 flight)	Stair climb (4 flights)	mPPT score
Book lift	1	.550**	.266**	.296**	.211*	.176	.420**	.471**	.371**	.528**
Jacket	.550**	1	.311**	.415**	.345**	.360**	.413**	.444**	.394**	.620**
Coin	.266**	.311**	1	.589**	.415**	.615**	.390**	.474**	.366**	.677**
50 ft walk	.296**	.415**	.589**	1	.611**	.645**	.563**	.727**	.658**	.855**
360 turn	.211*	.345**	.415**	.611**	1	.562**	.390**	.501**	.554**	.735**
Standing balance	.176	.360**	.615**	.645**	.562**	1	.458**	.497**	.522**	.757**
Chair rise	.420**	.413**	.390**	.563**	.390**	.458**	1	.529**	.504**	.730**
Stair Climb (1 flight)	.471**	.444**	.474**	.727**	.501**	.497**	.529**	1	.682**	.814**
Stair Climb (4 flights)	.371**	.394**	.366**	.658**	.554**	.522**	.504**	.682**	1	.786**
mPPT score	.528**	.620**	.677**	.855**	.735**	.757**	.730**	.814**	.786**	1

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)