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Greater Fatigue Resistance of Dorsiflexor Muscles in People with Prediabetes than Type 2 Diabetes

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Abstract

Although exercise can prevent progression to T2D among people with prediabetes, little is known about fatigue during exercise in people with prediabetes compared to T2D. The purpose of the study was to compare the magnitude and mechanisms of fatigability of the ankle dorsiflexor muscles between people with prediabetes and T2D. Ten people with prediabetes (6 females, 51.7 ± 6.9 years) and fourteen with T2D (6 females, 52.6 ± 6.2 years) who were matched for age, body mass index and physical activity performed an intermittent (6 s contraction: 4 s relaxation) fatiguing task at 75% maximal voluntary contraction (MVC) with the dorsiflexors. Electrical stimulation was used to assess contractile properties of the dorsiflexor muscles before and after the fatiguing task. People with prediabetes had a longer time-to-task failure, i.e. greater fatigue resistance (7.9 ± 5.1 vs. 4.9 ± 2.5 min, $P = 0.04$), and slower rate of decline of the (potentiated) twitch amplitude (6.5 ± 3.1 vs. 16.5 ± 11.7%·min^{-1}, $P = 0.03$) than people with T2D. Shorter time-to-task failure (i.e. greater fatigability) was associated with greater baseline MVC torque ($r^2 = 0.21$, $P = 0.02$) and faster rate of decline of twitch amplitude ($r^2 = 0.39$, $P = 0.04$). The ankle dorsiflexor muscles of males and females with prediabetes were more fatigue resistant than people with T2D, and fatigability was associated with contractile mechanisms.

Keywords

Recovery, Impaired glucose tolerance, Physical activity, Strength, Contractile properties

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronically elevated blood glucose levels (hyperglycemia) due to inadequate production of insulin or resistance to the action of insulin (American Diabetes, 2015). Approximately 95% of cases of diagnosed diabetes are type 2 diabetes (T2D) affecting over 8% of the world population (Collaboration, 2016). Prior to developing T2D, there is a clinical stage of intermediate hyperglycemia called *prediabetes* (American Diabetes, 2015). Glycated hemoglobin (HbA_{1c})—a crude estimate of average blood glucose over the previous 3–month time interval (Bode et al., 2007) — is one of the primary diagnostic criterion for diabetes (Roszyk et al., 2007) and is used to delineated between controls ($HbA_{1c} < 5.7\%$), people with prediabetes ($HbA_{1c} > 5.6\%$ and <6.5%) and people with T2D ($HbA_{1c} \geq 6.5\%$). Within four years of developing prediabetes, about one-third of people will progress to T2D; however, this high risk of developing T2D can be reduced by 50% with lifestyle interventions including exercise training (Knowler et al., 2002). To induce appropriate physiological adaptations in limb muscles, exercise training must incorporate an optimal balance between fatigability and adequate recovery after each bout of exercise (Kraemer and Ratamess, 2004).

Fatigability of skeletal muscle is a reversible, short-term and activity-induced reduction in muscle strength or power (Gandevia, 2001, Hunter, 2018), and can limit performance of daily tasks that require repeated or sustained contractions (Enoka and Duchateau, 2016, Senefeld et al., 2017). The magnitude of fatigability and the relative influence of the mechanisms that contribute to fatigability are dependent on the details of the task, and a better understanding of this phenomenon known as task dependency has remained a scientific priority since 1995 (Enoka, 1995, Hunter, 2018). The differences in fatigability between groups of people can also markedly vary with differing task demands, for example, older adults are *less* fatigable than young adults during low intensity isometric fatiguing contractions but *more* fatigable than young adults during high intensity dynamic fatiguing contractions (Christie et al., 2011). The limb muscles of people with diabetes (type 1 and type 2) are typically more fatigable than controls without diabetes for many different fatiguing tasks including isometric and dynamic contractions at maximal and submaximal intensities (Allen et al., 2015, Bazzucchi et al., 2015, Halvatsiotis et al., 2002, IJzerman et al., 2012, Petrofsky et al., 2005). Importantly, for dynamic fatiguing tasks with the knee extensor muscles, people with T2D were almost twice as fatigable as healthy controls even when the groups were matched for age, body mass index (BMI) and physical activity (Senefeld et al.,

2018, Senefeld et al., 2019b). Greater fatigability of people with T2D is associated with HbA_{1c} and contractile properties of the skeletal muscle (Senefeld et al., 2018, Senefeld et al., 2019b). However, little is known about the fatigability of people with prediabetes.

To-date one study showed that for dynamic contractions of the knee extensor muscles, people with prediabetes were less fatigable than those with T2D when matched for age, sex, BMI and activity levels (Senefeld et al., 2019a). Despite the functional relevance of isometric contractions, it is not known whether fatigability in people with prediabetes differs from those with T2D for an *isometric* fatiguing task. There is clinical relevance for determining the underlying contributions to muscle fatigue and the exercise limitations of limb muscles in persons with prediabetes for timely and enhanced management of disease progression (Praet and van Loon, 2008). Prediabetes presents an opportunity to intervene and halt the progression of the disease to T2D because fatigability of people with T2D has been associated with a loss of mobility, muscle strength, and quality of life (Ijzerman et al., 2011, IJzerman et al., 2012). Hence, we compared the limb fatigability of people with prediabetes and people who had already progressed to a diagnosis of T2D.

The *purpose* of this study was to compare fatigability and recovery of the ankle dorsiflexor muscles, and the neural and contractile mechanisms, for a high-force intermittent isometric fatiguing task in males and females with prediabetes and T2D who were matched for age, BMI and physical activity. Given the previously described correlations between fatigability and both skeletal muscle contractile mechanisms and HbA_{1c}, we *hypothesized* that people with prediabetes would have both greater fatigue resistance (longer time-to-task failure) and attenuated impairments in muscle contractile properties in response to the fatiguing task compared to people with T2D. Additionally, we *hypothesized* that people with prediabetes would have faster recovery of maximal muscle force and muscle contractile properties after the fatiguing task than people with T2D.

2. Methods

2.1. Ethical approval

Ten people with prediabetes (6 females and 4 males; age, 51.7 ± 6.9 years; HbA_{1c}, 6.13 ± 0.40%) and 14 people with T2D (6 females and 8 males; age, 52.6 ± 6.2 years; HbA_{1c}, 8.36 ± 1.28%) volunteered and provided written informed consent. All experimental procedures were approved by the University of Windsor Research Ethics Board (REB: 05-146) and conformed to the principles in the *Declaration of Helsinki*. People with prediabetes were pair-matched to people with T2D according to age, BMI and physical activity.

2.2. Experimental design

All participants were independent and community-dwelling adults. T2D was physician-diagnosed; the duration of T2D was 5.2 ± 4.4 years and confirmed at study enrolment via glucose and HbA_{1c} assays (see Table 1). People with prediabetes had HbA_{1c} ≥ 5.7% and <6.5% (American Diabetes, 2015), and all participants were otherwise healthy.

Table 1. Physical characteristics of men and women with prediabetes and T2D.

		Prediabetes		**T2D**		
		Males	**Females**	**Males**	**Females**	
Variable	**Units**	***n* = 4**	***n* = 6**	***n* = 8**	***n* = 6**	
Age	**years**	55.0 ± 4.7	49.5 ± 7.6	54.3 ± 6.6	50.5 ± 5.5	
Height	**cm**	174.8 ± 6.0	167.5 ± 4.9	181.0 ± 6.8	161.5 ± 6.9	†
Weight	**kg**	92.9 ± 12.7	103.4 ± 21.9	108.5 ± 18.5	93.3 ± 16.2	
Waist Circumference	**cm**	109.5 ± 7.9	114.3 ± 15.4	115.4 ± 14.8	107.2 ± 10.5	
BMI	**$kg \cdot m^2$**	30.3 ± 2.0	36.8 ± 7.5	33.0 ± 3.8	35.8 ± 5.7	†
MNSI	**AU**	3.5 ± 1.8	4.2 ± 2.1	4.0 ± 2.0	5.2 ± 1.2	

Monofilament	**n**	9.9 ± 0.3	10.0 ± 0.0	9.8 ± 0.5	9.8 ± 0.3	
HbA_{1c}	**%**	6.20 ± 0.36	6.08 ± 0.46	7.98 ± 0.34	8.87 ± 1.88	*
Physical Activity	**$hr \cdot wk^{-1}$**	20.6 ± 5.9	31.7 ± 10.2	24.6 ± 19.2	32.4 ± 17.4	
Leisurely Activity	**$U \cdot mo^{-1}$**	20.0 ± 18.3	19.2 ± 17.4	16.9 ± 18.5	14.0 ± 16.4	
Light Activity	**$U \cdot mo^{-1}$**	12.0 ± 10.3	14.0 ± 9.4	14.5 ± 15.3	16.0 ± 11.3	
MVC Torque	**Nm**	39.4 ± 2.3	26.3 ± 3.9	40.3 ± 9.2	29.6 ± 7.3	†
Twitch Amplitude	**Nm**	5.2 ± 1.1	3.9 ± 1.4	4.6 ± 1.2	3.6 ± 1.7	†
Time to Peak Torque	**ms**	98.5 ± 9.4	101.4 ± 14.1	96.6 ± 11.6	93.9 ± 9.0	
Half-Relaxation Time	**ms**	107.5 ± 12.0	104.0 ± 21.6	106.0 ± 11.5	119.6 ± 32.2	

Values are displayed as mean ± SD. BMI, body mass index; MNSI, Michigan Neuropathy Screening Index; AU, arbitrary unit; HbA_{1c}, glycated hemoglobin; hr, hour; wk, week; U, units; mo, month. Symbols next to the variable name indicate a significant effect of * group or † sex at $P < 0.05$.

Participants were excluded if they were enrolled in high-intensity exercise training more than three times per week. Participants were screened for physical activity participation using the self-report Yale Physical Activity Survey (Dipietro et al., 1993), which required them to estimate the time they spent doing specific activities over a typical 7-day period.

Participants completed two sessions of testing including a familiarization session and an experimental session, less than two weeks apart. During the familiarization session, each participant completed a consent form, sensory screening, the physical activity questionnaire, and a brief familiarization. During the experimental session, maximal strength, muscle contractile properties, fatigability of an intermittent isometric contraction sustained until failure, and 10 min of recovery of the ankle dorsiflexor muscles were assessed (as described below). All experiments were performed on the ankle dorsiflexor muscles of the non-dominant leg, except for three participants because they had knee joint surgery (*n* = 2 people with T2D) and prior muscle injury (*n* = 1 person with prediabetes); in these cases the dorsiflexors of the dominant leg was tested.

2.3. Familiarization session

2.3.1. Sensory screening

Each participant was screened for the presence of diabetic polyneuropathy using a questionnaire (Michigan Neuropathy Screening Instrument, MNSI) (Moghtaderi et al., 2006) and application of a 10 g Semmes-Weinstein monofilament (Neuropen, Owen Mumford Ltd., UK) to the dorsum of each foot, as performed previously (Senefeld et al., 2018, Singh-Peters et al., 2007). No participants were suspected of having diabetic polyneuropathy, i.e. MNSI scores ≤2 and the monofilament was readily sensed on all sites of testing.

2.3.2. HbA_{1c}

HbA_{1c} testing was performed using blood from a fingerstick, analyzed using a point-of-care instrument assay (A_{1c} Now Multi-test System, Metrika Inc., Sunnyvale, CA) certified by the National Glycohemoglobin Standardization Program (NGSP) (Bode et al., 2007). All tests were performed by one investigator (L.A.S.) using standardized and recommended techniques.

2.3.3. Familiarization procedures

Participants were instructed on all experimental procedures, habituated to electrical stimulation, and practiced maximal voluntary isometric contractions (MVCs), submaximal contractions, and the fatiguing task. Each procedure is detailed below in the experimental session.

2.4. Experimental session

Participants refrained from caffeine consumption for at least two hours prior to the experimental session. Participants completed preliminary electrical stimulation to determine the intensity of stimulation to be used during the session, performed three to five baseline MVCs with each followed by electrically-evoked twitch contractions to record contractile properties, performed a fatiguing task until failure followed by recovery measures of MVCs and electrically-evoked contractions for up to 10 min following the fatiguing task. See Fig. 1.

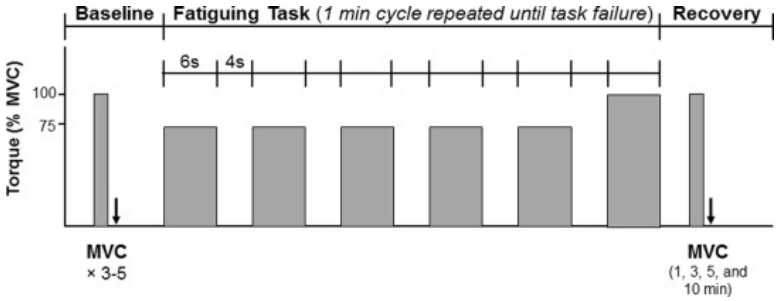

Fig. 1. **Experimental Protocol.** Schematic showing the experimental protocol of the experimental session. Shown are baseline measures of maximal voluntary contraction (MVC) and twitch contractile properties, for a fatiguing task (intermittent, isometric fatiguing task with 6 s contraction and 4 s relaxation cycles) and recovery measures. ↓ denotes electrical stimulation. [TTF, time-to-task failure]

2.4.1. Experimental set up

Participants were seated in a custom-instrumented isometric dynamometer with the ankle at 30° of plantar flexion, and the hip and knee joints positioned at 90° (midway between flexion and extension). Adjustable straps were tightened to restrict ancillary movements including one across the hips (secured to the dynamometer chair), one across the ankle (secured to the footplate) and one across the foot (secured to the footplate). The footplate was instrumented with a commercial load cell on the underside (Model MLP-500-T, Transducer Techniques, Inc., Temecula, CA) such that sagittal plane ankle flexion and extension (plantarflexion and dorsiflexion) were recorded. Analog signals from the load cell were amplified (1000x), filtered (60-Hz notch filter) (Model V72-25A, Coulbourn Instruments, Allentown, PA), digitized (1000 Hz) (model 1401, Cambridge Electronic Design Ltd., Cambridge UK), and analyzed offline (Spike2, Cambridge Electronic Design Ltd.).

2.4.2. Electrically-Evoked contractions

Single-pulse (100 µs duration, 400 V) percutaneous electrical stimulation (Digitimer Ltd., Hertfordshire, UK) via hand-held custom-made electrode bar was used to stimulate the peroneal nerve after visual inspection and palpation. The 4-cm anode-to-cathode bar electrode, was held in place by the operator over the common peroneal nerve slightly inferior and posterior to the fibular head. The optimal positioning of the probe was demarcated with indelible ink to ensure that the same electrode position was maintained throughout the duration of the experimental procedures. The intensity of stimulation was determined by increasing the current of the stimulator until the amplitude of the electrically-evoked twitch contraction plateaued. The stimulation current was then increased by 10% to ensure supramaximal stimulation and contractions were monitored to ensure there were no palpable or visible signs of antagonist (plantar flexor) activation.

2.4.3. Maximal voluntary isometric contractions (MVCs)

Participants completed at least three MVCs for ~5 s each with the dorsiflexor muscles, with three minutes rest between each MVC. Up to two additional MVCs (five total) were performed if the participant did not achieve two MVCs within 5%. Electrically-evoked, potentiated twitch contractions were also elicited via supramaximal electrical stimulation at rest immediately (within 1.0 s) after each MVC to determine contractile properties of the dorsiflexor muscles (see ‘data analysis’ section).

2.4.4. Fatiguing task and recovery

Participants performed an intermittent isometric fatiguing protocol involving repeated contractions at 75% MVC for 6 s each followed by 4 s of rest. Each minute, a 6-second MVC was performed to assess the change in maximal strength. Task failure was identified as a decline in MVC torque ≤75% baseline MVC, thus, the fatiguing protocol always ended with an MVC. Strong verbal encouragement was provided to continue until task failure. The sets of recovery contractions included one MVC followed by an electrically-evoked potentiated twitch contraction performed at the following time points: immediately after the fatiguing task, and then at 1, 3, 5 and 10 min after the fatiguing task.

2.4.5. Electromyography

Electromyography (EMG) electrodes (Ag–AgCl, 8-mm diameter; 20 mm inter-electrode distance) were placed on the tibialis anterior muscle belly in a bipolar arrangement according to recommendations (Hermens et al., 2000), with a reference electrode placed over the patella. The EMG signals were amplified (100×), filtered (13–1000 Hz band pass), and digitized (2000 Hz) through an analog-to-digital converter (Power 1401, Cambridge Electronics Design (CED), Cambridge, UK) and analyzed offline with custom algorithms using Spike2 software package (CED).

2.5. Data analysis

Contractile properties of the dorsiflexor muscles were quantified from the potentiated twitch elicited with electrical stimulation at rest. Peak twitch amplitude was determined as the maximal torque value elicited by the electrical stimulation. Time-to-peak torque was determined as the time interval elapsed from the electrical stimulus until the peak twitch amplitude. Half-relaxation time was determined as the time interval elapsed from the peak twitch amplitude until the torque reached 50% of the peak twitch amplitude.

Surface EMG signals were full-wave rectified and integrated [iEMG] over 0.5 s intervals for the middle 2 s of each MVC and each successive submaximal contraction after the MVC in each cycle of fatigue and recovery. The MVC and 75% iEMG for each cycle were normalized to the largest baseline MVC performed prior to the fatiguing task. To quantify fatigability, the changes in variables of the final fatiguing cycle were calculated as: (task end – baseline) × $(\text{baseline})^{-1}$ × 100% for the MVC torque, muscle contractile properties, and EMG. The average rate of fatigability was calculated using these values relative to the duration of the fatiguing task. To quantify recovery, the changes in variables during the 10-minute recovery were calculated (relative to task end) as: (Recovery10 – task end) × $(\text{task end})^{-1}$ × 100%. The average rates of recovery were calculated using these values (recovery) relative to the duration of recovery (10 min).

2.6. Statistical analysis

Assumptions of Normality were confirmed with Shapiro-Wilks tests and assumptions of homoscedasticity were confirmed with Levene's Test. Participant characteristics, baseline muscle function, and time-to-task failure were compared between groups (prediabetes, T2D) and sex (males, females) using one-tailed independent Student's *t*-tests to assess the directional hypotheses. To determine changes over time during the fatiguing task or recovery period, separate mixed model ANOVAs with group (prediabetes, T2D) and sex (males, females) as between subject factors and repeated measures over time was used for MVC torque, muscle contractile properties, and EMG.

Pearson correlation coefficients (*r*) were used to determine associations between variables including fatigability (time-to-task failure), participant characteristics (see Table 1), baseline muscle characteristics and measurements of fatigue-related changes in muscle properties (see Table 2). The *a priori* level of significance for all statistical comparisons was $P < 0.05$ except post hoc testing with Bonferroni corrections ($P < 0.025$), and all the analyses were performed in IBM Statistical Package for Social Sciences (SPSS) version 25. Exact *P* values and

estimated effect sizes (η) are reported in the text. Data are reported as mean ± SD in the text and displayed as mean ± SE in the figures.

Table 2. Changes in MVC torque and muscle contractile properties.

		Prediabetes	**T2D**	
	Units	***n* = 10**	***n* = 14**	
Time-to-Task Failure	**min**	7.9 ± 5.1	4.9 ± 2.5	*
MVC Torque				
Baseline	**Nm**	31.6 ± 7.5	35.7 ± 9.8	
Task End	**Nm**	24.1 ± 5.3	26.8 ± 7.6	
Recovery 10	**Nm**	28.0 ± 5.2	32.9 ± 8.7	
Fatigability Δ	**%**	−26.0 ± 9.3	−27.3 ± 5.2	
Fatigability Rate	**%·min^{-1}**	−4.1 ± 2.8	−7.4 ± 4.0	*
Recovery Δ	**%**	+12.4 ± 8.4	+17.2 ± 7.2	
Twitch Amplitude				
Baseline	**Nm**	4.43 ± 1.37	4.18 ± 1.45	
Task End	**Nm**	2.81 ± 1.39	1.66 ± 1.26	
Recovery 10	**Nm**	3.95 ± 0.85	2.39 ± 1.38	
Fatigability Δ	**%**	−44.0 ± 28.3	−61.9 ± 26.7	
Fatigability Rate	**%·min^{-1}**	−6.5 ± 3.1	−16.5 ± 11.7	*
Recovery Δ	**%**	+21.5 ± 18.6	+37.2 ± 22.6	
Time-to-Peak Torque				
Baseline	**ms**	100.2 ± 11.9	95.4 ± 10.3	
Task End	**ms**	119.1 ± 9.2	117.1 ± 36.4	
Recovery 10	**ms**	96.4 ± 13.6	89.5 ± 19.5	
Fatigability Δ	**%**	+21.1 ± 21.2	+22.5 ± 28.5	
Fatigability Rate	**%·min^{-1}**	+5.5 ± 6.7	+6.8 ± 8.5	
Recovery Δ	**%**	−23.9 ± 21.9	−30.7 ± 25.9	
Half-Relaxation Time				
Baseline	**ms**	105.4 ± 17.6	111.8 ± 22.8	
Task End	**ms**	140.1 ± 19.6	126.8 ± 28.9	
Recovery 10	**ms**	100.5 ± 13.7	98.5 ± 23.5	
Fatigability Δ	**%**	+11.4 ± 4.5	+13.9 ± 18.3	
Fatigability Rate	**%·min^{-1}**	+2.5 ± 1.3	+3.1 ± 6.0	
Recovery Δ	**%**	−25.3 ± 10.4	−29.2 ± 10.3	

Values are displayed as mean ± SD. MVC, maximal voluntary isometric contraction; ms, millisecond. Symbols next to the variable name indicate a significant effect of * group at $P < 0.05$.

3. Results

3.1. Baseline measurements

As anticipated, people with prediabetes had lower HbA_{1c} than people with T2D ($P < 0.01$,η = 0.60). See Table 1. Participants with prediabetes were not prescribed medication. One participant with T2D had no prescription medications, however, all other participants with T2D treated diabetes with Metformin (*n* = 8), insulin (*n* = 1) or both Metformin and insulin (*n* = 2).

People with prediabetes and T2D were not different in age ($P = 0.96$,η < 0.01), height ($P = 0.98$,η < 0.01), weight ($P = 0.72$,η = 0.01), waist circumference ($P = 0.91$,η < 0.01), BMI ($P = 0.72$,η = 0.01) or habitual physical activity ($P = 0.96$,η < 0.01). See Table 1.

3.2. Sex differences

There were anticipated sex-related differences in several baseline measurements (see Table 1 for sex and group effects). Males had larger MVC torque ($P < 0.01, \eta = 0.46$) and potentiated twitch torque ($P = 0.03, \eta = 0.27$) of the dorsiflexor muscles compared with females. However, there were no sex-related differences (main effects or interactions) in any measurements of fatigability or changes in contractile properties ($P > 0.05$).

3.3. Fatigability and recovery

MVC Torque: Baseline MVC torque was not different between people with prediabetes and T2D ($P = 0.27, \eta = 0.06$). The progressive reduction in MVC torque during the intermittent fatiguing task (time, $P < 0.01, \eta = 0.95$) was not different for people with prediabetes and T2D (time × group, $P = 0.74, \eta = 0.09$; Fig. 3A) per requirements for task failure (~25% reduction in MVC). However, people with prediabetes had a longer time-to-task failure, i.e. less fatigable ($P = 0.04, \eta = 0.14$), than the T2D group, and so the average rate of MVC torque decline during the fatiguing task was less for those with prediabetes than T2D ($P = 0.02, \eta = 0.18$). See Fig. 2.

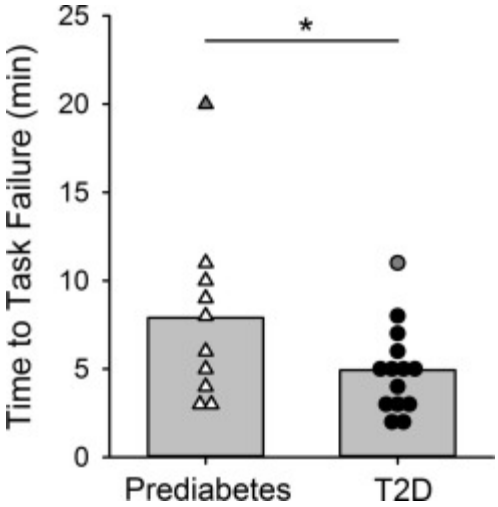

Fig. 2. **Time-to-task failure for intermittent isometric fatiguing task.** Time-to-task failure was longer for people with prediabetes (open triangles) than those with type 2 diabetes (T2D; filled circles). * indicates prediabetes > T2D, $P < 0.05$. [min, minutes]

MVC torque increased during the 10-minute recovery period after the fatiguing task (time, $P < 0.01, \eta = 0.98$) but was not different between people with prediabetes and T2D (time × group, $P = 0.31, \eta = 0.26$; group, $P = 0.15, \eta = 0.11$). Although time-to-task failure was considered a normal distribution for the prediabetes group ($W = 0.86, P = 0.07$) and T2D ($W = 0.91, P = 0.11$), visual inspection of boxplots identified one outlier within each group. Statistics were repeated with removal of these outliers, and the interpretation of the results did not change. For example, with the outliers removed, the prediabetes group had a longer time-to-task failure than people with T2D (6.6 ± 3.0 vs. 4.5 ± 1.9 min, $P = 0.03, \eta = 0.17$).

3.4. Muscle contractile properties

Baseline: Baseline contractile properties of the potentiated twitch were not different between people with prediabetes and T2D, including the potentiated twitch amplitude ($P = 0.67, \eta = 0.01$), time-to-peak torque ($P = 0.30, \eta = 0.05$) and half-relaxation time ($P = 0.47, \eta = 0.02$; Table 2).

Fatigability: During the fatiguing task, the reduction in potentiated twitch amplitude (time, $P < 0.01, \eta = 0.94$; time × group, $P = 0.04, \eta = 0.57$; Fig. 3B) was less for people with prediabetes than those with T2D, particularly during the last 25% of the fatiguing task. Thus, the average rate of decline in twitch amplitude from the initial

twitch to that at task end was slower for prediabetes group than T2D ($P < 0.01$,η = 0.61). However, the changes in other contractile properties during the fatiguing task were not different for people with prediabetes compared with T2D, including the increase in time-to-peak torque (time, $P < 0.01$,η = 0.29; time × group, $P = 0.97$,η = 0.01) and the increase in half-relaxation time (time, $P = 0.048$,η = 0.31; time × group, $P = 0.70$,η = 0.05). Also, the calculated rates of increase of the time-to-peak torque ($P = 0.78$,η = 0.01) and half-relaxation time ($P = 0.87$,η < 0.01) over the course of the fatiguing task were not different between people with prediabetes and T2D. See Fig. 3.

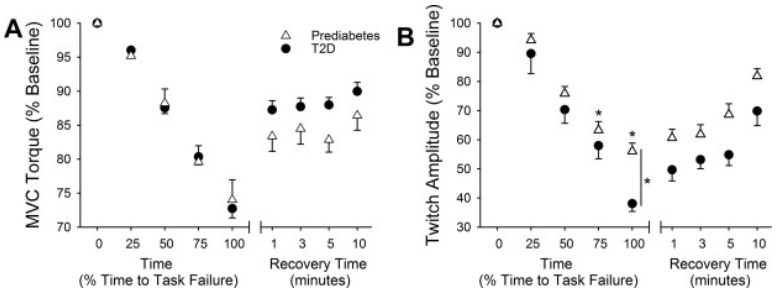

Fig. 3. **Fatigability during the intermittent isometric fatiguing task.** Muscle contractile properties during the fatiguing task and 10-minute recovery period for people with prediabetes and type 2 diabetes (T2D), including maximal voluntary isometric contraction (MVC) torque (A), potentiated twitch amplitude (B), potentiated twitch contraction time (C), and potentiated twitch half-relaxation time (D). * indicates prediabetes > T2D, $P < 0.05$.

Recovery: The changes in contractile properties of the dorsiflexor muscles during the 10-minute recovery period were not different between the prediabetes and T2D groups, including the increase in twitch amplitude (time, $P = 0.04$,η = 0.62; time × group, $P = 0.77$,η = 0.20; group, $P = 0.17$,η = 0.06), reduction of time-to-peak torque (time, $P < 0.01$,η = 0.37; time × group, $P = 0.41$,η = 0.09; group, $P = 0.37$,η = 0.06) and reduction of half-relaxation time (time, $P < 0.01$,η = 0.89; time × group, $P = 0.95$,η = 0.09; group, $P = 0.90$,η = 0.02). Similarly, during the 10-minute recovery, the rates of increase in twitch amplitude ($P = 0.29$,η = 0.16), decrease in the time-to-peak torque ($P = 0.63$,η = 0.02) and decrease in half-relaxation time ($P = 0.58$,η = 0.03) did not differ between people with prediabetes and T2D.

Electromyography (EMG): The progressive increase in EMG activity during the submaximal contractions ($P < 0.01$,η = 0.66) was not different between people with prediabetes and T2D ($P = 0.68$,η = 0.11). Similarly, the progressive decrease in EMG activity during the intermittent MVCs ($P < 0.01$,η = 0.28) was not different between people with prediabetes and T2D ($P = 0.60$,η = 0.03).

3.5. Bivariate correlations

The identified outliers for time-to-task failure were not included in bivariate correlation analyses. Time-to-task failure (fatigability) was associated with: 1) the average rate of decline in potentiated twitch amplitude ($r = -0.62$, $P = 0.04$) during the fatiguing task and 2) baseline MVC torque ($r = -0.46$, $P = 0.02$) (Fig. 4). Notably, time-to-task failure was not statistically associated with HbA_{1c} ($r = -0.41$, $P = 0.056$). Thus, those participants (groups pooled) who had the shortest time-time-to-task failure (i.e. greater fatigability) had the greatest baseline strength and the fastest rate of decline in the twitch amplitude.

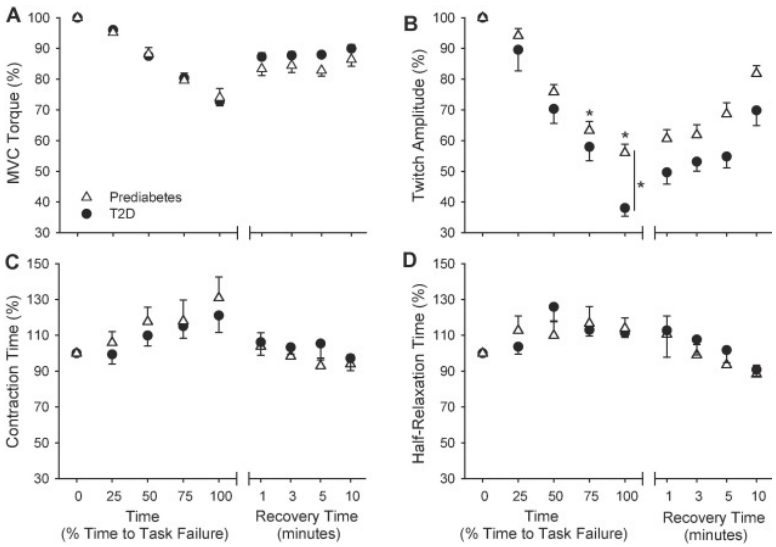

Fig. 4. **Associations with Fatigability.** Shorter time-to-task failure (i.e. greater fatigability) was associated with greater twitch torque fatigue rate (r = −0.62, P = 0.04) during the fatiguing task (A) and greater baseline MVC torque (r = −0.46, P = 0.02; B). The twitch torque fatigue rate (i.e. rate of decline in potentiated twitch amplitude) was calculated as the quotient of the magnitude of decline in the potentiated twitch amplitude (%; numerator) and the time-to-task failure (min; denominator). The two outliers for time-to-task failure were not included in the analyses.

4. Discussion

The novel findings of this study were that both males and females with prediabetes had: 1) longer time-to-task failure (i.e. greater fatigue resistance), 2) a slower rate of decline in the potentiated twitch amplitude, and 3) similar recovery in maximal strength and contractile properties of the ankle dorsiflexor muscles after a high-force isometric fatiguing task compared to people with T2D who were matched for activity levels. There were no differences in the increase in EMG activity of the submaximal contractions during the fatiguing task between people with prediabetes compared to those with T2D, suggesting that activation of the muscle did not contribute to greater fatigue resistance of people with prediabetes. Fatigability of the dorsiflexor muscles was associated with reductions in the potentiated twitch amplitude, providing evidence that fatigue resistance of people with prediabetes was due to smaller impairments in muscle contractile function during fatiguing exercise compared to people with T2D. These results support the general conclusion that greater fatigability of both males and females with T2D compared to people without T2D is primarily due to mechanisms impairing contractile function of the skeletal muscle, and that people with prediabetes have preserved fatigability of limb muscles compared to people with T2D.

4.1. Fatigability

Although there is growing evidence that control participants without diabetes have greater fatigue resistance of limb muscles than people with diabetes (type 1 or type 2) (Allen et al., 2015, Almeida et al., 2008, Bazzucchi et al., 2015, Halvatsiotis et al., 2002, IJzerman et al., 2012, Petrofsky et al., 2005, Senefeld et al., 2019a, Senefeld et al., 2018, Senefeld et al., 2019b), these data are the first to demonstrate greater fatigue resistance (longer time-to-task failure) in people with *prediabetes* compared to people with T2D. Both groups in this current study are classified as having similar and low physical activity levels (lightly active) based on the physical activity questionnaire scores (Dipietro et al., 1993). Our current findings are also consistent with previous findings of greater fatigue resistance in *active* people with prediabetes than those with T2D after a dynamic fatiguing task (Senefeld et al., 2018). Together, these findings suggest that persons with prediabetes have greater fatigue resistance than matched persons with T2D whether active or inactive. Although increased physical activity can

offset fatigability in people with prediabetes and T2D (Colberg et al., 2010), recent data suggests that both groups (prediabetes and T2D) have greater fatigability than healthy controls (Senefeld et al., 2019a). Together these studies indicate that greater fatigability of limb muscles is progressive with the more advanced stage of diabetes mellitus, and should be considered when evaluating muscle function, and treatment of dysglycemia.

4.2. Mechanisms of fatigability

The mechanisms contributing to the reduction in dorsiflexion MVC torque during the isometric fatiguing task were altered contractile function of the dorsiflexor muscles, with minimal evidence for altered ability to activate the muscle for either group. The increase in surface EMG amplitude represents a net increase in motor unit activity and muscle activation of the tibialis anterior during the fatiguing contraction primarily due to increased motor unit recruitment and altered discharge rates of the motor unit (Enoka and Duchateau, 2008). Because the net change in EMG activity did not differ between the groups, recruitment strategies and activation of the muscle did not appear to differ between the prediabetes and T2D groups, and thus potentially did not contribute to the slower rate of fatigability in people with prediabetes. However, surface EMG represents a crude estimate of net motor unit activity (Enoka, 2019), which incorporates complex interactions of excitatory and inhibitory input from descending efferent input, spinal interneurons and peripheral afferent feedback. Emerging evidence suggests that people with T2D have lower and more variable motor unit discharge frequency compared to controls (Senefeld et al., 2020, Watanabe et al., 2013) which is exacerbated with increased muscle activity (Watanabe et al., 2012). The interaction between motor unit activity and fatigability in people with T2D and prediabetes was not precisely defined in the current investigation and the contribution of the motor unit to greater fatigability of people with T2D warrant future investigations.

In contrast to activation strategies, the average rate of decline of the electrically-evoked twitch torque during the fatiguing task was markedly less for people with prediabetes than those with T2D (6 vs.16%·min^{-1}), although the time-to-peak and half-relaxation time of the potentiated twitch were not different between groups. As commonly observed during fatiguing tasks (Enoka and Stuart, 1992), there was a prolongation of twitch contractile properties which may have contributed to maintenance of high relative forces despite the large decrease in twitch amplitude. The mechanical properties of electrically-stimulated skeletal muscle provide insight to the cellular mechanisms contributing to fatigability during exercise *in vivo* (Kent-Braun et al., 2012). The reduction of twitch *torque* is thought to be due to an additive effect of fatigue-induced metabolic by-product accumulation, blunted calcium (Ca^{2+}) sensitivity and blunted Ca^{2+} transients (Debold et al., 2016). Whereas, the reduction of the twitch *kinetics*, indicating slowed cross-bridge detachment rates, are primarily indicative of Ca^{2+} transients (Westerblad et al., 1998). Thus, the present data suggest that reduced metabolic by-product accumulation or reduced sensitivity to metabolites and/or Ca^{2+} in people with prediabetes compared to those with T2D probably contributes to the greater fatigue resistance in people with prediabetes. The precise roles of metabolic by-products and Ca^{2+} activity and Ca^{2+} transients on fatigability during exercise however, remain a topic of debate (Fitts, 2016, Westerblad, 2016), and is an area of opportunity for future studies in people with prediabetes and T2D. Although it has been demonstrated that Ca^{2+} uptake and Ca^{2+}-ATPase activity were higher before and after a fatiguing task in humans with type 1 diabetes (with mild hypoinsulinemia) and under resting conditions in rodents with streptozotocin-induced diabetes (Ganguly et al., 1986, Harmer et al., 2014), these are models of absolute or relative hypoinsulinemia. However, in people with prediabetes and T2D in which insulin resistance with mild or marked hyperinsulinemia are present, the effects on Ca^{2+} transients during fatigue are unknown and warrant future investigation.

4.3. Recovery

People with prediabetes demonstrated similar recovery of MVC torque, electrically-evoked twitch contractile properties and EMG amplitude compared to people with T2D measured at 1, 3, 5 and 10 min after the fatiguing task. Even after 10 min of recovery, however, neither group (prediabetes, T2D) was fully recovered to baseline

levels in maximal strength or twitch properties. Similarly, our previous findings demonstrate impaired recovery in people with T2D compared to matched controls after dynamic fatiguing contractions (Senefeld et al., 2018). The MVC torque was ~90% of baseline (Fig. 3A) and the electrically-evoked, potentiated twitch torque was ~80% of baseline for both groups combined (Fig. 3B). During a 3-s MVC, intracellular Ca^{2+} kinetics likely have minimal impact on peak torque produced because MVCs are produced by sustained, rapid muscle activation generating a fused, tetanic state of force at the plateau of the force-frequency relationship. Thus, it is likely that the observed ~10% impairments in MVC peak torque after the 10-minute recovery is due to blunted Ca^{2+} sensitivity and/or a reduced number of high-force cross-bridges (Allen et al., 2008, Debold et al., 2016). However, the reduction in electrically-evoked twitch amplitude after the 10-minute recovery (20%) was likely due to an additive effect of prolonged Ca^{2+} kinetics (Cheng et al., 2018), blunted Ca^{2+} sensitivity and a reduced number of high-force cross-bridges (Allen et al., 2008, Debold et al., 2016).

4.4. Conclusion

Males and females with prediabetes were matched for age, body mass index and nominal physical activity levels to people with T2D, and demonstrated less fatigability and slower declines of MVC torque and electrically-evoked twitch amplitude of the dorsiflexor muscles. There were no group-related differences in baseline contractile properties (MVC torque and electrically-evoked contractile properties) and there was no difference in the increase in EMG during the fatiguing task between people with prediabetes and T2D. Additionally, time-to-task failure was associated with baseline MVC strength and the reduction in dorsiflexor contractile properties. These data suggest that contractile mechanisms rather than activation of the muscle are responsible for the greater fatigability in people with T2D than those with prediabetes. Importantly, there were no group-related differences in recovery of MVC torque or the contractile properties. We propose that recovery from fatiguing exercise is impaired in people with prediabetes and T2D (compared to controls and our previous work (Senefeld et al., 2018)), however, fatigability during exercise is exacerbated to a lesser extent in people with prediabetes than those with T2D.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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