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Lower Physical Activity Is Associated With Higher Intermuscular Adipose Tissue in People With Type 2 Diabetes and Peripheral Neuropathy

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Lower Physical Activity Is Associated With Higher Intermuscular Adipose Tissue in People With Type 2 Diabetes and Peripheral Neuropathy

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Background. Increased lipid accumulation in skeletal muscle has been linked to insulin resistance, impaired muscle performance, and impaired physical function. It is unclear whether physical activity is associated with lipid content in skeletal muscle, muscle performance, or overall physical function.

Objective. The purpose of this study was to characterize physical activity levels (average daily step count) in a sample of people with diabetes and peripheral neuropathy and to determine the relationship among step count, intermuscular adipose tissue volume (IMAT), muscle performance (peak torque, power), and physical function.

Design. A cross-sectional design was used in this study.

Methods. Twenty-two people with diabetes and peripheral neuropathy (15 men and 7 women, mean age=64.5 years [SD=12.7], and mean body mass index=33.2 kg/m^2 [SD=6.4]) participated. Average daily step count, glycosylated hemoglobin, modified 9-item Physical Performance Test scores, Six-Minute Walk Test distance, calf intermuscular adipose tissue volume (via magnetic resonance imaging), and isokinetic dynamometry of the ankle muscles were recorded.

Results. Average daily step count was 7,754 (SD=4,678; range=3,088–20,079). Five participants had an average daily step count greater than 10,000. Average IMAT volume was 84 cm^3 (SD=88). Greater average daily step count was associated with younger age ($r=-.39$, $P<.05$) and with lower IMAT volume in the calf ($r=-.44$, $P<.05$). Lower IMAT volume was associated with greater muscle performance ($r=-.45$) and physical function ($r=-.43$ to $-.48$).

Limitations. The sample in this study may be biased toward people with high levels of activity because participants were recruited for an exercise study. The results should not be generalized to people taking fewer than 3,000 steps/day or to those with a current foot ulcer, peripheral arterial disease, or severe foot deformity or amputation or who weigh more than 136 kg (300 lb).

Conclusions. Average daily step count was inversely related to IMAT, and IMAT was inversely related to muscle performance and overall physical function. In addition, we found that people with diabetes and peripheral neuropathy and without severe foot deformity appear to be able to take a large number of steps per day.

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Diabetes mellitus is a chronic disease that affects almost 24 million people, with 60% to 70% developing nervous system impairments, including peripheral neuropathy.[1] Increased physical activity has been shown to decrease pain and improve balance, including in people with diabetes and peripheral neuropathy.[2] Improved physical activity is particularly important for people with diabetes, not only for improved glucose control and cardiovascular fitness, but also because they are twice as likely as people without diabetes to have limitations in physical mobility, particularly in the presence of peripheral neuropathy.[3]

The mechanisms for physical mobility limitations in people with diabetes are unclear, but previous work has demonstrated that people with diabetes, peripheral neuropathy, and obesity have an increased amount of adipose tissue (ie, fat) in the muscles of the lower extremity that is not noted in their peers and that this increased intermuscular adipose tissue is associated with poor physical functional status.[4] *Intermuscular adipose tissue* (IMAT) is defined as the visible extracellular adipose tissue that is located beneath the muscle fascia and between and within muscle groups.[5] The mechanism by which IMAT potentially impairs physical function is unclear, but decreased muscle strength (force-generating capacity) and power have been associated with an increased amount of IMAT in the calf and thigh muscles of people with diabetes and peripheral neuropathy, thereby suggesting increased IMAT as a mechanism for impaired physical function.[4,6] Intermuscular adipose tissue has been linked to immobilization in young adults who are healthy[7] and has been shown to be reduced with exercise in a population with diabetes and without peripheral neuropathy,[8] indicating that physical activity may be a potent modifier of IMAT content in skeletal muscle. Intermuscular adipose tissue also has been shown to be higher in the affected limb in people with chronic stroke[9] and spinal cord injury[10] and those with rotator cuff injury with nerve involvement,[11] indicating that nerve dysfunction (such as peripheral neuropathy) could affect IMAT. In addition, IMAT has been associated with insulin resistance,[12] suggesting that it may contribute to or worsen the metabolic impairments of skeletal muscle that accompany diabetes. It is important, therefore, to determine whether IMAT is influenced by physical activity, specifically walking, and if so, whether increases in physical activity are associated with greater muscle performance, glucose control, and physical function in people with diabetes mellitus and peripheral neuropathy.

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The purpose of this study was to characterize activity levels (average daily step count) in people with diabetes and peripheral neuropathy and to determine the relationship between activity level and IMAT volume in the calf, calf muscle volume, muscle performance, physical function, and glucose control. The American Diabetes Association recommends that people take 10,000 steps/day,[13] but we hypothesized that people with diabetes and peripheral neuropathy would take approximately 5,000 steps/day based on prior observations and reports.[14–16] We hypothesized that higher average daily step count would be associated with lower IMAT volume, larger muscle volume, improved glucose control (lower glycosylated hemoglobin [HbA1c] levels), better muscle performance, and better physical function.

Method

Participants

Twenty-two people with type 2 diabetes and peripheral neuropathy (15 men and 7 women, mean age 64.5 years [SD=12.7], and mean body mass index [BMI]=33.2 kg/m^2 [6.4]) were recruited for this study as part of a larger study involving exercise for people with diabetes and peripheral neuropathy from the Washington University School of Medicine Diabetes Clinic and from diabetes clinics in the surrounding St Louis area. Participants were excluded if they weighed more than 136 kg (300 lb) (equipment weight limit), had a history of severe foot deformity or amputation, or had any comorbidity or medications that would interfere with exercise (eg, severe rheumatoid arthritis, peripheral arterial disease [absent pulses], dialysis, current cancer treatment). Participants were excluded if they had a current foot ulcer; 2 of the 22 participants had a history of a previous foot ulcer that had been healed for at least 6 months. All participants provided written informed consent.

Assessments

Peripheral neuropathy. Presence of peripheral neuropathy was determined based on an inability to feel the 5.07 Semmes-Weinstein monofilament on at least 1 point on the plantar surface of the foot and on a vibration perception threshold of greater than 25 V as measured with a biothesiometer.[16,17]

Activity monitoring. For the purposes of this study, "activity level" refers specifically to average daily step count as recorded by a Step-

Watch activity monitor.* Participants were given an activity monitor and were instructed to wear the monitor around their ankle during all waking hours. The participants were given the monitor for at least 9 consecutive days, calculating an average of 7 days. The first and last days of wear were excluded from the analysis because a full 24 hours would not be recorded. For a day to be included, the monitor had to be worn for at least 8 hours, and at least 1 weekend day was included in the 7-day average. The device records strides per day, and steps per day were calculated by multiplying strides by 2 (1 stride equals 2 steps). Results of validity tests performed in our laboratory indicate a mean absolute error of 1.1% (SD=3.1%) for participants who were obese but otherwise healthy and 1.8% (SD=2.4%) for participants with diabetes mellitus and peripheral neuropathy.[16]

Six-Minute Walk Test. All participants performed the Six-Minute Walk Test (6MWT)[18] as a measure of physical function and walking endurance, which was validated previously in adults who were obese.[19] The participants walked back and forth in a hallway between 2 cones that were placed 100 feet† apart. The participants were told that the goal was to walk as far as possible in 6 minutes; the test was not repeated. The 6MWT score was recorded as total distance walked in feet.

Physical Performance Test. The modified 9-item Physical Performance Test (PPT) was used to assess physical function in all participants. The 9-item PPT is designed to mimic activities of daily living, and scores have been shown to correlate well with disability and frailty.[20–22] Each of the items is scored on a scale of 0 to 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 to 4 score. A maximum score is 36.

Intermuscular adipose tissue. Intermuscular adipose tissue volumes were quantified with magnetic resonance imaging (MRI) on the right leg of each participant using previously established methods.[4] 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-T superconducting MRI instrument‡ with a pulse sequence of TE=12 milliseconds, TR=1,500 milliseconds, matrix=256 × 256. 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, with voxel size of 0.7 × 0.7 × 7 mm. The 15 center consecutive slices were selected to calculate muscle and IMAT volumes. Volumes were quantified using a PC workstation and Analyze Direct software version 9.0,§ which uses voxel brightness to distinguish between muscle and adipose tissues.[5] 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) remained. On a subset of 10 participants, intraclass correlation coefficient (2,1) values of the same scan by the same observer averaged .98 when scans were measured at least 7 days apart.

Ankle dorsiflexion and plantar-flexion peak torque and power. Concentric isokinetic ankle dorsiflexion and plantar-flexion peak torque and power as measures of muscle performance were assessed using a Biodex Multijoint System 3

* Orthocare Innovations, 840 Research Parkway, Suite 200, Oklahoma City, OK 73104.
† 1 ft=0.3048 m.

‡ Siemens Corp, Citicorp Center, 153 E 53rd St, New York, NY 10022.

§ Mayo Clinic, 200 First St SW, Rochester, MN 55905.

The Bottom Line

What do we already know about this topic?

Some research indicates that people with diabetes and peripheral neuropathy are less active and have more potentially harmful intermuscular adipose tissue (IMAT) than their peers.

What new information does this study offer?

This study reports that a higher average daily step count is associated with lower levels of IMAT in people with diabetes and peripheral neuropathy and that some people with diabetes and peripheral neuropathy are able to have high average daily step counts.

If you're a patient, what might these findings mean for you?

Some people with diabetes and peripheral neuropathy are able to maintain high levels of physical activity, which is associated with lower levels of potentially harmful IMAT.

Table 1.
Group Characteristics According to Average Daily Step Count[a]

Step Count (Steps/Day)	N	Sex (Male/Female)	Age (y)	BMI (kg/m²)	HbA1c	Duration of Diabetes (y)	Vibration Perception Threshold (V)	Average Step Count (Steps/Day) [95% CI]	IMAT (cm³)	Muscle Volume (cm³)	PPT	6MWT (ft)	PFPT (ft·lb)
<5,000	7	4/3	68 (14)	35.5 (6.7)	7.0 (1.2)	11 (6)	42 (10)	3,995 (624) [3,533–4,457]	157 (127)*	735 (206)	26 (5)	1,147 (300)*	33.3 (12.5)
5,000–8,000	8	6/2	69 (10)	30.5 (6.1)	6.9 (0.4)	11 (9)	39 (11)	6,310 (1,032) [5,595–7,025]	53 (27)	811 (253)	30 (2)	1,564 (244)	42.7 (10.5)
>8,000	7	5/2	55 (11)*	33.9 (6.2)	7.4 (2.2)	11 (7)	40 (11)	13,162 (4,645) [9,721–16,603]	44 (22)	880 (66)	29 (3)	1,471 (346)	44.1 (7.9)
P values[b]			.05	.30	.78	.98	.86	<.00**	.02	.40	.07	.04	.13
Full range	22	15/7	65 (13)	33.2 (6.4)	7.1 (1.4)	11 (7)	40 (10)	7,754 (4,678) [5,799–9,708]	84 (88)	809 (196)	28 (4)	1,402 (336)	40.1 (11.1)

[a] Values are mean (SD) unless otherwise indicated. BMI=body mass index, HbA1c=glycosylated hemoglobin, 95% CI=95% confidence interval, IMAT=intermuscular adipose tissue volume in the calf, PPT=modified 9-item Physical Performance Test score, 6MWT=Six-Minute Walk Test distance in feet (1 ft=0.3048 m), PFPT=plantar-flexion peak torque in foot-pounds (1 ft·lb=1.356 N·m). *Indicates difference from other 2 groups based on *post hoc t* tests from analysis-of-variance results ($P<.05$). **Indicates all 3 groups were different from each other based on *post hoc t* tests from analysis-of-variance results ($P<.05$).
[b] *P* values are from the analysis-of-variance results among the 3 groups based on activity level.

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 ankle joint range of motion.[4] 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.

Data Analysis

Statistical analyses were performed using Systat for Windows, version 13.0.[#] Pearson correlation coefficients were used to determine the association between variables. Multiple regression analysis was performed, with average step count as the dependent variable and IMAT volume, age, BMI, HbA1c, duration of diabetes, muscle performance (dorsiflexion and plantar-flexion peak torque and power), and physical performance (6MWT distance and PPT score) as the independent variables. Statistical significance was set at $P<.05$. *Post hoc*, the 22 participants were divided into 3 groups based on step count in an effort to determine whether there were differences among people who were taking more steps than the group mean (>8,000 steps/day), those who were in our expected range for step count (5,000–8,000 steps/day), and those whose step count was lower than expected (<5,000 steps/day). A 1-way analysis of variance was performed, with age as a covariate to determine differences in IMAT volumes that were caused by group differences in activity level. Analyses of variance also were performed to determine differences in IMAT volume, muscle volume, mus-

‖ Biodex Medical Systems, 20 Ramsay Rd, Shirley, NY 11967.
Systat Software Inc, 225 W Washington St, Suite 425, Chicago, IL 60606.

Table 2.
Multiple Regression Analysis Results for Step Count as Dependent Variable[a]

Variable	*R*	R^2	R^2 Change	Significant F Change
IMAT volume	.44	.19	.19	.04
Age	.51	.26	.07	.19
BMI	.53	.28	.02	.51
HbA1c	.61	.38	.10	.13
Diabetes duration	.61	.38	.00	.84
Muscle performance[b]	.63	.39	.01	.90
Physical performance[c]	.74	.55	.16	.17

[a] IMAT=intermuscular adipose tissue, BMI=body mass index, HbA1c=glycosylated hemoglobin.
[b] Muscle performance=dorsiflexion and plantar-flexion peak torque and power.
[c] Physical performance=Six-Minute Walk Test distance and modified 9-item Physical Performance Test scores.

cle performance, PPT scores, and 6MWT distance based on group differences in activity level (Tab. 1). Statistical significance was set at $P<.05$.

Results

Average daily step count for these 22 participants with diabetes and peripheral neuropathy ranged from 3,088 to 20,079, with an average of 7,754 (SD=4,678). Participant characteristics are listed in Table 1. In order to characterize the people who were more active and those who were less active, the participants were categorized into 3 groups based on average step count (<5,000 steps/day, 5,000–8,000 steps/day, and >8,000 steps/day) (Tab. 1). The group that was taking fewer than 5,000 steps/day had 3 times the volume of IMAT in their calf muscles compared with the groups that were taking 5,000 to 8,000 steps/day and more than 8,000 steps/day ($\overline{X}=157$ cm^3 [SD=127] vs $\overline{X}=53$ cm^3 [SD=27] vs $\overline{X}=44$ cm^3 [SD=22], respectively; $P<.05$). However, the more active group also was younger than the other 2 groups (Tab. 1). Therefore, a 1-way analysis of covariance also was performed, with IMAT volume as the dependent variable, step count as the independent variable, and age as a covariate. Results were unchanged, and IMAT volumes remained significantly different ($P=.03$) among the groups.

A multiple regression analysis was used to determine the variance in average step count accounted for by IMAT volume, age, BMI, HbA1c, diabetes duration, muscle performance, and physical function (Tab. 2). The IMAT volume accounted for 19% of the variance in average step count ($P=.04$). The other independent variables did not account for a significant portion of the variance in IMAT volume in this sample ($P>.05$).

Activity as indicated by average step count was associated with age ($r=-.39$) and with IMAT volume ($r=-.44$), but average step count was not associated with glucose control (as indicated by HbA1c), muscle

Table 3.
Univariate Correlation Matrix[a]

Variable	Steps	MVol	HbA1c	PPT	6MWT	IMAT	DFPT	DFPOW	PFPT	PFPOW	DM DUR	VPT
Age	−.39*	−.46*	−.54*	−.15	−.22	.31	−.20	−.12	−.23	−.21	−.04	.36
Steps		.23	−.12	.27	.10	−.44*	.05	−.02	.19	.18	−.09	−.03
MVol			.35	.09	.17	−.45*	.69*	.65*	.36	.12	−.02	−.03
HbA1c				−.18	.04	−.11	.20	.15	.12	.05	.22	−.39*
PPT					.75*	−.43*	−.03	−.08	.55*	.43*	−.36	−.08
6MWT						−.48*	.08	.03	.47*	.48*	−.27	−.06
IMAT							−.06	−.02	−.45*	−.29	−.05	−.16
DFPT								.97*	.37	.14	.03	.03
DFPOW									.28	.02	.00	.10
PFPT										.82*	−.35	−.02
PFPOW											−.43*	−.08
DM DUR												−.01

[a] Steps=average daily step count, MVol=muscle volume in the calf, HbA1c=glycosylated hemoglobin, PPT=modified 9-item Physical Performance Test score, 6MWT=Six-Minute Walk Test distance, IMAT=intermuscular adipose tissue volume in the calf, DFPT=dorsiflexion peak torque, DFPOW=dorsiflexion power, PFPT=plantar-flexion peak torque, PFPOW=plantar-flexion power, DM DUR=duration of time with diabetes, VPT=vibration perception threshold (measure of neuropathy). *Indicates significance at $P<.05$.

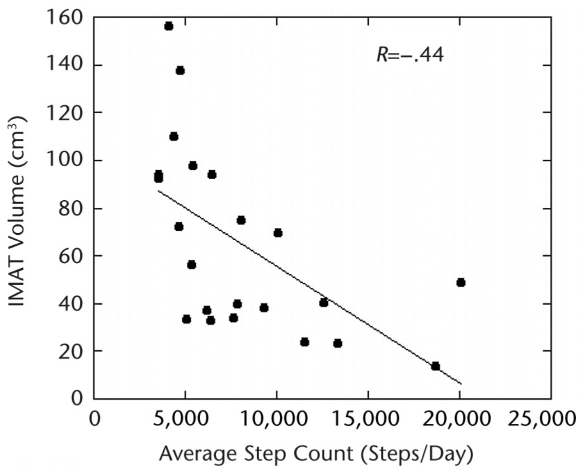

Figure.
Average step count versus intermuscular adipose tissue (IMAT) volume.

performance, muscle volume, or physical function ($P>.05$) (Tab. 3). The IMAT volume was associated with select indicators of muscle performance (plantar-flexion peak torque: $r=-.45$, $P=.03$) and physical function (PPT score: $r=-.43$, $P=.04$; 6MWT distance: $r=-.48$, $P=.02$) and with average step count ($r=-.44$, $P=.04$).

Discussion

This study is the first to demonstrate an inverse relationship between physical activity levels and IMAT volume in the calf muscle of people with diabetes and peripheral neuropathy. We also have demonstrated a significant relationship among increased IMAT volume, lower muscle performance, and physical function. This finding is in agreement with that of previous investigators who found that increased IMAT was associated with lower muscle performance,[4,6,12] suggesting that IMAT may be a potential pathway for intervention to mitigate the impairments associated with diabetes and peripheral neuropathy. However, these data provide only an association among these variables and do not imply causation. More studies are needed to elucidate the role of IMAT in these processes. In addition, these findings lead us to question whether increasing physical activity could decrease IMAT volume and improve physical function in people with diabetes mellitus and peripheral neuropathy.

Intermuscular adipose tissue volume also has been linked to insulin resistance[23–26] in people with metabolic syndrome and in those with frank diabetes. The exact relationship between IMAT and insulin resistance is not yet understood, but there is some evidence that weight loss[27] and exercise[28–30] can decrease the amount of IMAT and improve insulin sensitivity. It is unknown whether these same effects on IMAT in response to exercise and weight loss would be demonstrated in people with diabetes and peripheral neuropathy.

We hypothesized that higher average daily step count would be associated with less IMAT volume, larger muscle volume, improved glucose control, higher muscle performance, and higher physical function. This study showed that average daily step count was inversely correlated with IMAT volume, but step count was not correlated with glycemic control, muscle volume, muscle performance, or measures of physical function. Intermuscular adipose tissue volume was inversely correlated with muscle performance (plantarflexion peak torque) and with measures of physical function (PPT score and 6MWT distance). These findings suggest that activity could be a modifiable factor with the potential to affect muscle morphology (IMAT volume) and, therefore, improve physical function. The people who were the least active had 3 times the volume of IMAT in the calf as the people who were most active, on average (Tab. 1). Physical activity has been associated with IMAT volume in a population of young and healthy individuals,[7] but this is the first study showing that activity was associated with IMAT volume in a population with diabetes and peripheral neuropathy. These results provide evidence for a potential way not only to affect the metabolic disturbance of diabetes but also to improve the functional deficits that have been shown to occur in people with diabetes and peripheral neuropathy. Indeed, Marcus et al[8] demonstrated that people with type 2 diabetes were able to improve performance, decrease fat, and increase lean tissue in the thigh after a 16-week exercise program that included both aerobic and eccentric exercise training.

Additional studies are needed to determine whether more-intensive interventions targeted to increase activity or muscle strength can improve muscle and physical function in people with diabetes and peripheral neuropathy. Whereas the relationship between average step count and IMAT volume was significant, there also was great variability in IMAT volume, particularly in people with a lower step count (Figure). As noted in our multiple regression analysis, IMAT accounted for only 19% of the variation in step count, and there are many other factors that could be contributing to the variability seen in both IMAT and step count. More studies are needed to determine the variety of factors that affect IMAT volume.

In our previous work,[4] we found that people with diabetes, peripheral neuropathy, and obesity had a greater IMAT volume in their calf muscles than their age-matched peers who did not have diabetes or peripheral neuropathy and who were not obese. In our previous study, IMAT volume was related to muscle performance and function. However, we did not have measures of activity level in our previous study. The findings in this study that IMAT volume was associated with muscle performance and function are consistent with our previous results and expand upon this previous work to include activity level as a factor that may influence muscle performance and physical function. The results suggest that activity is associated with muscle morphology and could potentially be a way to improve the impaired physical function that accompanies chronic diabetes.

Based on previous studies, we hypothesized that people with diabetes and peripheral neuropathy would be taking approximately 5,000 steps/day.[15,16] We hypothesized this because, generally, the expectation is that people with diabetes and peripheral neuropathy are less active than their peers. However, the group for this study had an average daily step count of 7,919, and there were 5 people with diabetes and peripheral neuropathy who were taking more than 10,000 steps/day. The average step counts in this study are consistent with those from Maluf and Mueller[16]; however, they are significantly higher than those reported by Armstrong et al.[15] Because we were recruiting for an exercise study, our sample may have been biased toward people with high activity levels and limited our ability to recruit participants who were less active.

Surprisingly, HbA1C levels were not associated with activity. This finding is in conflict with other reports in the literature indicating that exercise and increased physical activity will improve glucose control.[31] There are several potential explanations for our finding that increased physical activity was not associated with improved glucose control. First, the participants in this study were not participating in a regular exercise program; the activity measure is a measure of regular daily walking activity. Intensity of exercise is a key factor in maintaining blood glucose control, and perhaps normal daily walking, regardless of total number of steps, does not reach an intensity level that is consistent with regulating blood glucose over the previous 3- to 4-month period that HbA1c indicates. Also, one limitation of this study is that we do not have any information on diet for these participants, and it is possible that dietary habits contributed more to overall HbA1c values than low-intensity physical activity in this particular sample. It also is possible that some of the participants in this study were not adherent in taking their daily medication, which also could adversely affect HbA1c values.

Although this study provides important information about the role of activity in people with diabetes and peripheral neuropathy, there are limitations that should be considered. First, the participants in this study were all interested in participating in an exercise study, so it is possible that our sample was biased toward those who tend to be more active. It is unclear whether our results are generalizable to people who are taking fewer than 3,000 steps/day. In addition, we excluded people who had a current foot ulcer, peripheral arterial disease, or severe foot deformity or amputation or who weighed more than 136 kg. Our results should not be generalized to these populations. There is evidence that walking capacity and performance decrease in the presence of severe foot deformity or amputation.[32] Additional research is needed to clarify the contraindications and safety precautions for a walking program or weight-bearing exercise program, given various levels of foot deformity and impairment. Also, based on these data, we can only say that step count and IMAT volumes are associated, but we cannot specify causation.

In conclusion, physical activity is associated with IMAT volume, and IMAT volume is related to muscle performance and overall physical function. In addition, we found that people with diabetes and peripheral neuropathy, but without severe foot deformity, appear to be able to take a large number of steps per day. More evidence is needed to determine whether an exercise program designed to increase step count will decrease the amount of IMAT volume and enhance muscle performance and physical function.

All authors provided concept/idea/research design and writing. Ms Tuttle provided data collection. Ms Tuttle and Dr Mueller provided data analysis. Dr Sinacore and Dr Mueller provided project management and facilities/equipment. Dr Mueller provided fund procurement and institutional liaisons. Dr Sinacore, Dr Cade, and Dr Mueller provided consultation (including review of manuscript before submission).

This study was approved by the Human Research Protection Office at Washington University, St Louis, Missouri.

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