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Research article

Bedside tests of muscle mass in older adults with Type 2 diabetes

Running title: Bedside measures of muscularity

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Abstract: Objective: Diabetes and sarcopenia often coexist in older adults, suggesting a possible bidirectional association. Available bedside measures of muscle mass consist of bedside ultrasound (MT, quadriceps muscle thickness) and Bioelectrical Impedance Analysis (BIA). We examined the association between ultrasound measures and BIA measures of muscle in older adults with measures of strength, performance and frailty in older adults with diabetes. **Design:** Cross-sectional study. **Methods:** 81 subjects (age ≥ 65; mean age 80.8 ± 0.6 years, 27 women, 53 men) were recruited sequentially from geriatric medicine clinics. Each subject had Lean Body Mass (LBM, by BIA, in kg), grip strength, gait speed, Cardiovascular Health Study index (frailty) and MT (in cm) measured. All initial models were adjusted for biological sex. **Results:** In our final parsimonious models, only MT (as opposed to LBM) showed a significant correlation with grip strength (Standardized $\beta = 0.217 \pm 0.078$; $p = 0.007$) and frailty (Standardized $\beta = 0.276 \pm 0.109$; $p = 0.013$). Neither MT or LBM showed a significant association with subject performance (gait speed). **Conclusions:** Unlike BIA, bedside ultrasound measures of muscle thickness showed strong associations with both grip strength and frailty in the older adult population with diabetes, suggesting that bedside measures of MT might be a more clinically useful modality to assess muscularity in this patient population. Neither BIA or MT measures of subject muscularity showed any association with our performance indicator (gait speed).

Keywords: sarcopenia; bedside ultrasound; bioelectrical impedance analysis; diabetes; geriatric medicine; frailty

Abbreviations: DXA: Dual-energy X-ray absorptiometry; LBM: Lean body mass; BIA: Bioelectrical impedance analysis; CHS Index: Cardiovascular health study Index; MT: Quadriceps muscle tissue thickness; AIC: Akaike's Information Criterion; Hg_{A1c}: Glycated hemoglobin; BMI: Body mass index

1. Introduction

It is well documented that throughout our lifespan we lose both muscle mass and function, a process known as sarcopenia [1]. Older adults that meet criteria for sarcopenia [2] are more likely to be hospitalized, and have 3 times the fall risk over a period of 2 years as compared to non-sarcopenic older adults [3]. Previous work done in the United States has shown that sarcopenia has an additional cost to the healthcare system of 26 billion dollars per year [4], a cost that will only increase with an aging population [4].

Sarcopenia manifests as a loss of muscle strength (dynapenia) [5], a loss of performance (such as gait speed) [6] and frailty [7]—three distinct clinical syndromes that can show significant overlap, although fraily can exist in the absence of sarcopenia. Diabetes is an independent risk factor for physical limitations [8], perhaps due to the fact that diabetes and sarcopenia are two conditions that often co-exist. A Korean study has demonstrated that subjects with diabetes have a three times higher risk of having this condition [9] and Leender et al has suggested that some of the processes that underlie sarcopenia might also underlie the pathophysiology of diabetes [10]. Given this context, it would be ideal to be able to screen for this condition at the bedside. Most definitions of sarcopenia rely on Dual-energy X-ray absorptiometry (DXA) measures of lean body mass (LBM) [2] which poses difficulties for bedside care since these scans are not portable and are not approved in most countries for conditions other than osteoporosis [11]. Computed tomography (CT) scans of the lumbar spine have also shown some value in diagnosing sarcopenia [12], but most clinical guidelines do not recommend the use of CT scans for this purpose [2]. Potential bedside screening modalities include ultrasound measures of muscle thickness [13] and bioelectrical impedance analysis (BIA) [14] but previous studies have shown that increased fatty liver and fluid shifts in the setting of diabetes can significantly alter BIA measures of muscularity in this vulnerable population [15–17].

To further investigate the clinical usefulness of these measures, our current study examined the association between 2 bedside measures of muscle mass (BIA and bedside ultrasound) with measures of strength (grip strength), performance (gait speed) and frailty (Cardiovascular Health Study Index, CHS Index) in an older adult population with type 2 diabetes. We hypothesized that an ultrasound-based measure would show a stronger association with measures of strength, performance and frailty than BIA measures of lean body mass in a population of older adults with diabetes.

2. Materials and methods

2.1. Subjects

The study design was an observational, cross-sectional study. All subjects were recruited from outpatient older adults diabetes clinics (Vancouver General Hospital, Vancouver, Canada) as part of a larger study examining sarcopenia in older adults from March 15th, 2019 to November 1st, 2019 (ClinicalTrials.gov, NCT04370912) [13,18]. All were referred by a primary care physician and were 65 years of age or over. Patients on hemodialysis were excluded, due to the possibility of fluid shifts

during therapy. Patients taking oral corticosteroids were excluded, due to the possibility of steroid-induced muscle atrophy. Subjects with pitting edema, severe dehydration, systemic central nervous system atrophies, paresis of the lower limbs, hemiparesis due to a stroke, systemic connective tissue disorders and central nervous system demyelinating diseases were excluded. Any subjects with peripheral edema due to liver, heart or renal failure were also excluded. Diabetes was defined as per current guidelines [19]. Peripheral edema was defined as having pitting edema on exam. Liver, heart and renal failure were defined as having these conditions diagnosed in the past, or having abnormal liver function/renal function on lab work in the patient's chart.

All subjects gave written consent and our study protocol received approval by the Human Subjects Committee of the University of British Columbia.

2.2. Muscle mass measures—(Muscle thickness, MT; Lean body mass, LBM)

After a 15 minute rest period, while lying supine, each subject had quadriceps muscle tissue thickness (MT) measured, with their knees resting in extension. Landmarking was done as per current standards [20], at a point 50 percent between the greater trochanter and the lateral condyle. All measures were done by a single operator (BF) using a bedside ultrasound device (Vscan with Dual Probe, GE Healthcare, IL). All images were obtained in B-mode, allowing cross-sectional imaging of the femoral quadriceps, on the dominant side as per current standards [20]. On-screen calipers were used to measure the MT distance [20]. Muscle thickness (MT) was measured using the calipers and consisted of the sum of the thickness of the rectus femoris and the vastus intermedius muscle. Gain was kept constant during all scans. SA (our academic lead for the Point of Care Ultrasound program instructed BF in all measures prior to data collection.

A HBF-510W Full Body Composition Monitor (Omron, Seoul, Korea) was utilized to measure LBM with bioelectrical impedance. We chose the quadriceps muscle as our measurement site due to the fact that ultrasound measures of muscle at this site have shown strong associations with both strength [21,22] and frailty measures [22] in previous studies of older adults.

2.3. Strength measure—Grip strength

Handgrip strength was measured using the dominant hand three times and then the values were averaged using a grip strength dynamometer (Sammons Preston, Nottinghamshire, UK).

2.4. Performance measure—Gait speed

Gait speed was measured as the mean velocity over 6 meters on a level surface. Gait speed testing was from a standing start, with an additional 2 meters for acceleration and 2 meters for deceleration. Subjects were given instructions to walk at their usual pace. Velocity was measured in meters per second using the Shimmer 2R device (*Kinesis Health Technologies,* Ireland).

2.5. Frailty measures—Cardiovascular health study index

The CHS frailty index was recorded in each subject; the CHS index utilizes a 5-point multidimensional scale consisting of low physical activity, slow walking speed, weakness, unintentional weight loss and subjective symptoms of exhaustion [23].

2.6. Statistical methods

Our outcome variables consisted of a measure of muscle strength (grip strength), a performance measure (gait speed), and a measure of frailty (the CHS index). Our predictor variables were age, biological sex, body mass index (BMI), and MT/LBM. *A priori* power analysis indicated that we required a sample size of 80 to achieve 80% power for detecting a small effect size (0.15), at a significance criterion of $\alpha = 0.05$. We logarithmically transformed (base ten) any predictors that demonstrated skewing prior to all analyses. After our initial model, model simplification was accomplished through a stepwise method, by removing the least significant predictor with a p-value of greater than 0.10. The Akaike's Information Criterion (AIC) was calculated after each predictor was removed [24]. Variance inflation factors were examined for multicollinearity. The R core software package version 4.0.0 was used for statistical analysis with a significance level of $p < 0.05$ [25]. The format mean ± standard error was used to express results, and all data analysis was done in a blinded fashion.

3. Results

3.1. Subject characteristics

81 subjects (27 women and 53 men, mean age 80.8 ± 0.6) were recruited. One subject (1 woman) dropped out of the study prior to completing all measures. 3 subjects identified as South Asian, 11 as East Asian and 66 as White. All subjects had a diagnosis of Type 2 diabetes for at least 5 years. Mean body mass index (BMI) was 27.1 ± 0.6, waist circumference was 95.2 ± 2.1. The mean glycated hemoglobin (Hg_{A1c}) was 7.4 ± 0.01 percent. Mean MT was 2.1 ± 0.1 cm, mean LBM was 21.6 ± 0.5 kg, mean grip strength was 25.4 ± 0.9 kg and mean gait speed was 0.85 ± 0.03 m/s. The average CHS index was 1.5 ± 0.1 (out of a five point scale). 48 ± 6% of our subjects were on insulin, 26 ± 5% of our subjects were on sulfonylureas, 57 ± 6% were on metformin and 46 ± 6% were on other oral agents, such as glitazones. Of the 80 subjects, 13 subjects were not frail (0 criteria), 51 were pre-frail (1 or 2 criteria) and 16 were frail.

Subject characteristics stratified by biological sex are presented in Table 1.

Prior to analysis, all predictor variable density plots were inspected; no skewing was detected and no transformation was required prior to the analyses. Prior to our multivariable analyses, variance inflation factors showed no issues with multicollinearity (all were less than a conservative threshold of 2) [26].

Table 1. Subject characteristics in women and men.

Measure	Women Mean (SE)	Men Mean (SE)	p Value
Age (years)	80.5 (0.9)	80.9 (0.7)	0.781
Body mass index (kg/m^2)	27.7 (1.1)	26.8 (0.6)	0.45
Waist circumference (cm)	92.5 (4.7)	96.6 (2.0)	0.352
Glycated hemoglobin (percent)	7.5 (0.2)	7.6 (0.2)	0.796
MT (cm)	1.9 (0.1)	2.0 (0.1)	0.542
LBM (kg)	17.2 (0.8)	23.8 (0.4)	<0.001
Grip strength (kg)	18.8 (1.0)	28.8 (0.9)	<0.001
Gait speed (m/s)	0.87 (0.06)	0.83 (0.04)	0.574
CHS index (5 point scale)	1.5 (0.2)	1.5 (0.2)	0.969

Note: SE: Standard error; MT: Muscle thickness; LBM: Lean body mass; MT: Muscle thickness; CHS: Cardiovascular health study.

3.2. Univariate analysis (Table 2)

MT and LBM demonstrated a significant positive correlation with each other ($p = 0.007$). MT demonstrated a significant positive correlation with grip strength ($p = 0.007$) but no significant association with gait speed ($p = 0.356$). With respect to measures of frailty, MT demonstrated a negative association with the CHS index ($p = 0.013$). Our univariate analysis of LBM measures demonstrated a significant positive correlation with grip strength ($p < 0.001$) but no significant association with gait speed ($p = 0.693$). LBM did not show any significant associations with the CHS index ($p = 0.914$).

3.3. Multivariable analysis—Grip strength

Our initial model containing age, BMI, MT and biological sex initially explained 54% of the variation in grip strength, and demonstrated a significant positive association with MT (Standardized $\beta = 0.255 \pm 0.087$, $p = 0.005$, Figure 1). Our most parsimonious model with grip strength as our outcome variable demonstrated a significant associations with MT (Standardized $\beta = 0.217 \pm 0.078$; $p = 0.007$), age (Standardized $\beta = -0.217 \pm 0.078$; $p = 0.007$), and male biological sex (Standardized $\beta = 1.317 \pm 0.163$; $p < 0.001$).

For our BIA measure, our initial model containing age, BMI, LBM and biological sex initially explained 50% of the variation in grip strength, but demonstrated no significant association with LBM (Standardized $\beta = 0.222 \pm 0.161$, $p = 0.172$). Our most parsimonious model with grip strength as an

outcome variable only demonstrated significant associations with age (Standardized β = −0.239 ± 0.081; p = 0.004), and male biological sex (Standardized β = 1.353 ± 0.169; p < 0.001).

3.4. Multivariable analysis—Gait speed

Our initial model containing age, BMI, MT and biological sex initially explained 8% of the variation in gait speed, but demonstrated no significant association with MT (Standardized β = 0.096 ± 0.127, p = 0.450). Our most parsimonious model with gait speed as an outcome variable a demonstrated significant association with age only (Standardized β = −0.261 ± 0.110; p = 0.020).

For our BIA measure, our initial model containing age, BMI, LBM and biological sex initially explained 7% of the variation in gait speed, but demonstrated no significant association with LBM (Standardized β = −0.041 ± 0.224, p = 0.857). Our most parsimonious model with gait speed as an outcome variable a demonstrated significant association with age only (Standardized β = −0.261 ± 0.110; p = 0.020).

Table 2. Univariate analysis, correlations with muscle thickness (MT).

Measure (n = 80)	LBM, β (SE) p-value	MT, β (SE) p-value
Age (years)	−0.067 (0.224), p = 0.56	−0.099 (0.224), p = 0.386
Body Mass Index (kg/m^2)	0.456 (0.159), p ≤ 0.001*	0.455 (0.158), p ≤ 0.001*
CHS index (5 point scale)	0.012 (0.219), p = 0.914	−0.277 (0.216), p = 0.013*
Grip strength (kg)	0.468 (0.156), p < 0.001*	0.301 (0.187), p = 0.007*
Gait speed (m/s)	−0.045 (0.222), p = 0.693	0.105 (0.212), p = 0.356
MT (cm)	0.302 (0.187), p = 0.007	-

Note: LBM: Lean body mass; MT: Muscle thickness; β: Standardized beta coefficient; SE: Standard error; *: p < 0.05; CHS: Cardiovascular health study.

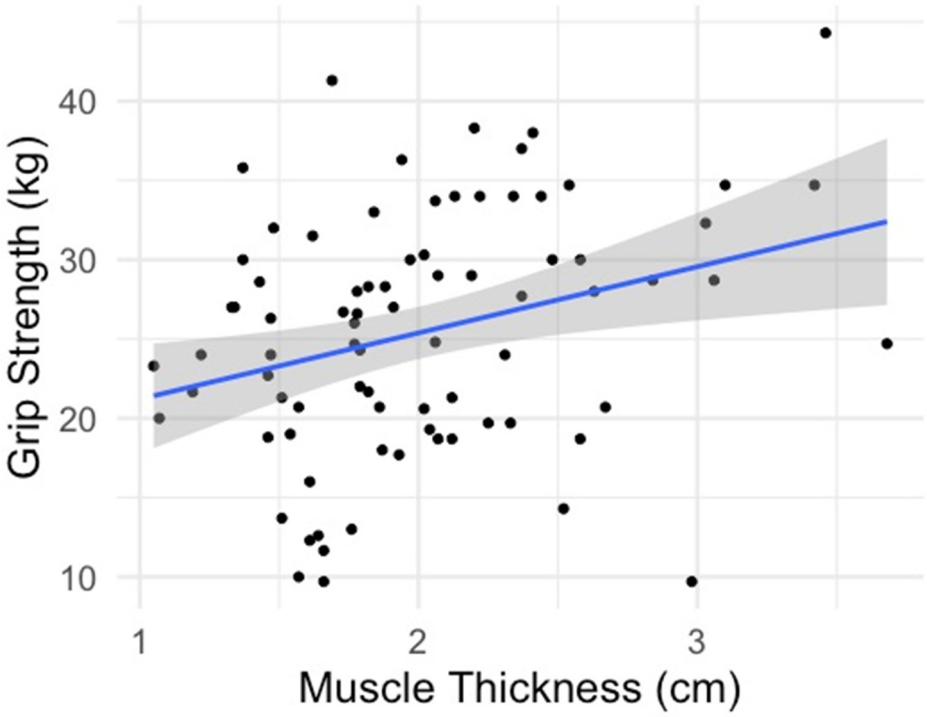

Figure 1. Association between Quadriceps Muscle thickness (MT) and Grip strength: We were able to demonstrate a significant association between MT and grip strength ($p = 0.007$ in adjusted model) in our older adult subjects with diabetes ($n = 80$). Linear regression is shown, with 95% confidence limits.

3.5. Multivariable analysis—Cardiovascular health study index

3.5.1. Muscle thickness

Our initial model containing age, BMI, MT and biological sex) initially explained 9% of the variation in the CHS index, demonstrating a significant association with MT (Standardized $\beta = -0.274 \pm 0.125$, $p = 0.032$, Figure 2). Our most parsimonious model with the CHS index as an outcome variable a demonstrated significant association with MT only (Standardized $\beta = 0.276 \pm 0.109$; $p = 0.013$).

3.5.2. Lean body mass

Our initial model containing age, BMI, LBM and biological sex initially explained 4% of the variation in the CHS index, demonstrating a significant association with LBM (Standardized $\beta = 0.180 \pm 0.226$, $p = 0.427$). Our most parsimonious model with the CHS index as an outcome variable a demonstrated significant association with age (Standardized $\beta = 0.161 \pm 0.112$; $p = 0.154$) only.

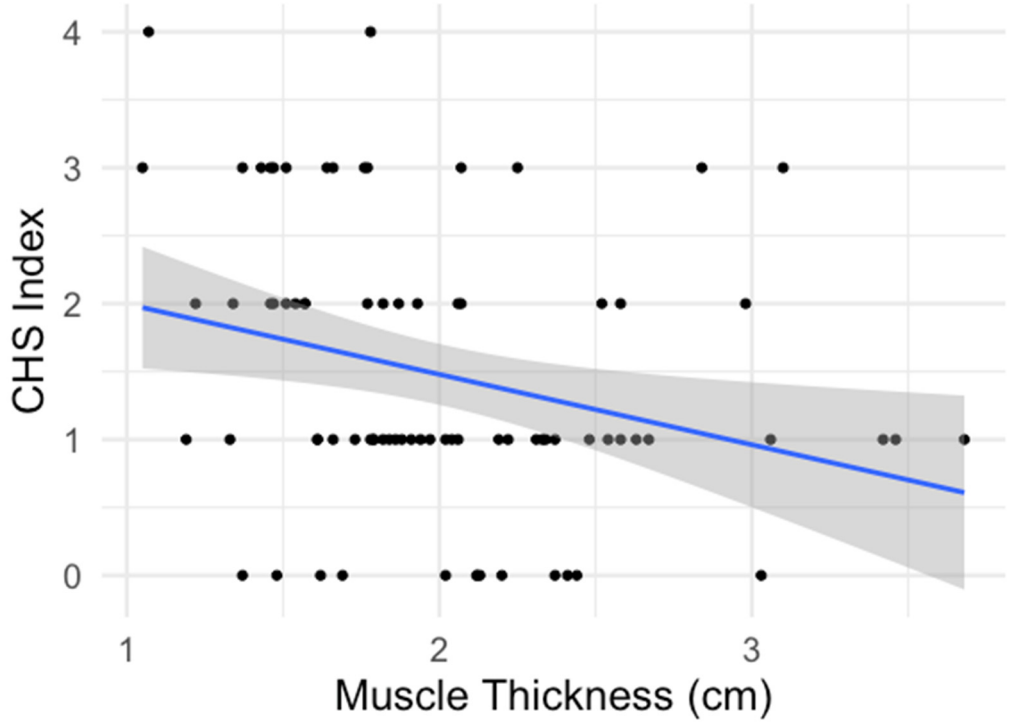

Figure 2. Association between Quadriceps Muscle thickness (MT) and Frailty: There was a significant association between MT and the Cardiovascular Health study (CHS) index (p = 0.013 in adjusted model) in our older adult subjects with diabetes (n = 80). Linear regression is shown, with 95% confidence limits.

4. Discussion

4.1. Principal findings

Our multivariate analysis demonstrated that only bedside ultrasound measures of muscle mass showed associations with muscle strength (grip strength) and frailty (CHS scale) in older adults with Type 2 diabetes, while no association was found with bedside BIA measures of muscle mass. Neither bedside modality showed a significant association with our performance measure (gait speed).

It is well established that having a diagnosis of diabetes increases your risk of developing physical limitations/reduced level of function [8]. The diagnosis of diabetes [9] increases the risk three-fold of having sarcopenia and the duration of diabetes is associated with an increase in the rate of decline in muscle mass [10,27]. Some have theorized that this acceleration in age-associated muscle loss in diabetes is due to a decrease in protein synthesis in response to anabolic stimuli in a state of insulin resistance [28]. Due to the probable bidirectional overlap in some of the mechanisms underlying both diabetes and sarcopenia [10,28,29] it has been suggested that interventions that target sarcopenia, such as resistance training and diet modifications should be routinely employed in older adults with both conditions [29,30]. A simple bedside test, such as BIA or bedside ultrasound would be an efficient and inexpensive method to measure muscle mass in these vulnerable patients.

Bedside ultrasound is becoming increasingly established as a technique to answer specific questions immediately at the point of care. Although this was initially pioneered in the emergency

room setting, this approach has steadily expanded to encompass bedside assessment of common clinical conditions such as synovitis [31], volume status [32], and spleen size [33]. Previous work in a community-based sample of older adults have shown associations between ultrasound measures of muscularity and measures of frailty, congruent with the results of our study in a population of older adults with diabetes [21,22,34]. Although bedside measures of muscle mass show promise in assessing patients for sarcopenia, some recent survey studies of physicians have identified lack of training, cost of the device, lack of credentialing and a lack of reimbursement as a barrier to their widespread adoption [35].

Although BIA is widely used to estimate "muscularity", this method does not actually measure a specific area of the body, instead relying on calibration equations developed from other methods such as computed tomography scans, magnetic resonance imaging or dual-energy x-ray absorptiometry [14]. Previous investigations in subjects with diabetes have shown that diabetes can result in significant fluid shifts (as indicated by elevated brain natriuretic peptide) that resulted in significant measurement errors [16]. In addition, the presence of significant liver fat in subjects with diabetes also can greatly influence BIA measures [15]. These findings are congruent with the results of the current study, which demonstrated no association between BIA measures of muscularity and either grip strength or frailty in older adults with type 2 diabetes. Our findings suggest that bedside measures of MT might be a more clinically useful modality to assess muscle mass and strength in this patient population.

Although bedside ultrasound measures of MT showed strong correlations with both measures of frailty and grip strength, neither BIA or MT showed any association with our performance measures (gait speed). Although it is well established that subjects with sarcopenia have lower gait speeds [36], there are numerous other factors that can reduce this performance indicator. Other factors such as cognitive changes [37], age, cardiometabolic risk factors, brain volume and cerebral microvascular changes [38] can also influence gait speed. In diabetes patients specifically, other issues such as the progression and extent of peripheral neuropathy [39] and ulcers [40] can result in slower gait velocity. A lack of association between bedside muscularity measures and gait speed is congruent with previous work [13]; the well established use of gait speed as an independent predictor of mortality in older adults [41,42] suggests that this easily measured clinical sign should be used to complement bedside measures of muscle mass, such as MT.

4.2. Clinical implications

Sarcopenia is well recognised as predictive of increased health care costs [4], increased mortality [43,44], reduced quality of life and increased morbidity [45] in the older adult population. In addition to the well established impact of nutrition [46] and the benefits of resistance training [47] there are currently several new pharmacological therapies in animal trials [48] that could potentially help older adults with diabetes complicated by concurrent sarcopenia. Sarcopenia as a condition remains chronically neglected as diagnosis, mainly due to the fact that the standard criteria [2] are rarely performed clinically (grip strength) or are impossible to perform at the bedside (DXA scanning). Given the increasingly recognized bidirectional relationship between diabetes and sarcopenia, a simple bedside test for loss of muscle such as MT could open up new avenues of intervention for older adults with diabetes [29]. An awareness of the possible different usefulness of MT and BIA in the older adult population with diabetes could greatly impact future screening criteria for future randomized

controlled trials in this population. On the other hand, training and technique operator-related variability in these measures [35] suggests that these measures might be more useful as a method of longitudinally following patients, as opposed to being useful as a single measure.

4.3. Limitations and future research

All subjects were recruited from an older adult diabetes clinic, suggesting our findings might not be applicable to the wider population. The clinics that were our recruitment sites get a large number of referrals from the emergency department, often due to the fact that the patient does not have a family physician; since men tend to not have a community physician at higher rates than women [49] we had more men than women in our subject pool. We also only measured MT at a single site, it is possible that other anatomical locations might provide more accurate measures in this population. Although bedside measures of MT show promise as a method to measure muscle mass in persons with diabetes, more work needs to be done to validate these measures, such as comparing these measures with more gold standard measures such as DXA scanning. Also the ability of these measures to detect the progression of sarcopenia over time requires further investigation.

5. Conclusions

Unlike BIA, bedside ultrasound measures of muscle thickness (MT) showed strong associations with both grip strength and frailty in the older adult population with diabetes. Neither BIA or MT measures of subject muscularity showed any association with our performance indicator (gait speed).

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Conflict of interest

All authors declare no conflicts of interest in this paper. The sponsor (the Allan M. McGavin Foundation) had no role in the study design, analysis or writing of the paper.

Authors' contributions

Kenneth Madden designed the study, gathered the raw data, performed the data analysis, wrote the manuscript, and edited the manuscript; Boris Feldman gathered the raw data and edited the manuscript; Shane Arishenkoff participated in study design, reviewed the ultrasound images and edited the manuscript; Graydon S. Meneilly participated in study design and editing the manuscript.

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