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Title: Extensor Digitorum Brevis Bulk and Associations with Fibular Motor Nerve Conduction Amplitude.

Short running title: EDB bulk is associated with fibular CMAP amplitude

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Abstract:

Introduction: Prior work demonstrates that fibular compound motor action potential (CMAP) amplitude < 4.0 mV predicts impairment of ankle proprioceptive precision and increased fall risk. Extensor digitorum brevis (EDB) inspection may present a simple clinical surrogate for CMAP amplitude.

Objective: 1) To estimate the inter-rater reliability of assessment of EDB bulk. 2) To determine whether inspection of EDB bulk is associated with fibular CMAP amplitude.

Design: Independently and prior to nerve conduction studies (NCS), two investigators graded EDB bulk. Next, fibular NCS were completed.

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Setting: An academic center's outpatient Physical Medicine & Rehabilitation EMG clinics.

Participants: 52 adult participants (102 feet)

Predictor: EDB bulk graded as 1)normal, 2)diminished, or 3)atrophied

Main Outcome Measures: 1. Inter-rater reliability of assessment of EDB bulk. 2. Mean fibular CMAP amplitude. 3. A binary measure of fibular CMAP amplitude above or below a 4.0 mV threshold.

Results: Inter-rater reliability of EDB bulk grading was moderate (kappa: 0.65 [95% C.I. 0.48 - 0.82]). The mean CMAP value was 5.9 ± 2.2 mV when bulk was normal, 3.4 ± 2.1 mV when diminished, and 0.6 ± 0.9 mV when atrophied. A multivariable analysis demonstrated that EDB bulk, distal symmetric polyneuropathy (DSP), and lumbar radiculopathy were all associated with CMAP amplitude. The sensitivity and specificity of grading muscle bulk as normal vs abnormal in detecting CMAP amplitude above or below 4.0mV were 0.86 [95% C.I. 0.78 – 0.94] and 0.71 [95% C.I. 0.54 – 0.88], respectively. An atrophied EDB was a highly specific indicator that CMAP amplitude was abnormal (< 4.0 mV) in 100% of cases (8/8).

Conclusions: EDB bulk was associated with fibular CMAP amplitude. Atrophy was a highly specific indicator for CMAP amplitude below 4.0 mV. Evaluation of EDB bulk may represent a quick and easy clinical surrogate marker for CMAP amplitude and distal neuromuscular impairment.

Key Words: Extensor digitorum brevis, fibular CMAP amplitude

Introduction:

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Falls are the leading cause of injuries, both fatal and non-fatal, among patients 65 and older in the United States[1]. Despite increasing research in fall prevention, the incidence rate of falls has increased annually between 2000 and 2016[2]. Easily predicting who is at risk for falls and who might benefit from more intensive intervention remains an important healthcare goal.

While it is well recognized that a distal symmetric polyneuropathy (DSP) increases risk of falls[3], individuals may have functionally relevant decline in nerve function years before meeting electrodiagnostic criteria for DSP[4], which highlights the importance of developing early markers for sub-optimal peripheral neurologic function. Reduced fibular nerve compound motor action potential (CMAP) amplitudes obtained by nerve conduction studies (NCS) may be one such marker, as they are associated with fall risk[5] and mobility disability[6,7]. Additionally, fibular CMAP amplitudes correlate robustly with ankle proprioception thresholds ($R2 = .591$, $p < .001$), with amplitudes $\geq$ 4 millivolts (mV) correlating with better proprioception [8]. This is clinically relevant because ankle proprioception explains nearly 25% of unipedal balance variance, and when ankle proprioception is combined with hip strength as a ratio, about 70% of unipedal balance variance is accounted for[9]. Furthermore, the hip strength to ankle proprioception ratio predicts both fall risk and injuries from falls[10]. The deep branch of the fibular nerve innervates the extensor digitorum brevis (EDB) muscle, an intrinsic foot muscle commonly used to evaluate the fibular nerve CMAP. The superficial anatomical position of the EDB makes it ideal for easy clinical inspection.

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The aim of this study was to determine the inter-rater reliability of clinical inspection of EDB muscle bulk, and whether EDB muscle bulk is associated with fibular nerve CMAP amplitude. If so, this would allow EDB muscle bulk to serve as a surrogate marker for the integrity of distal neuromuscular function, and simple inspection of the muscle bulk might provide insight into fall risk.

Methods:

Subjects: Subjects were recruited from outpatient Physical Medicine and Rehabilitation electrodiagnostic clinics at an academic center. This prospective study was approved by the institutional review board, and all patients provided written informed consent. Eligible subjects included all patients $\geq$ 18 years of age who were scheduled for an electrodiagnostic study and were capable of providing consent in English. Exclusion criteria included BMI > 40, pitting pedal edema, and inability to tolerate nerve conduction studies.

If a patient was scheduled to undergo NCS of the bilateral lower limbs, the study was performed as planned. For patients who were scheduled to undergo NCS of only the upper limbs, or of only one lower limb, the previously planned NCS for clinical purposes were completed first. The patients were then given the opportunity to drop out of the study if they preferred not to proceed with the additional study NCS for any reason. One patient, who was scheduled for a study of the left lower limb, dropped out of the study prior to undergoing NCS of the right lower limb due to discomfort (this patient's left lower limb data was included in the analysis). If a patient did wish to proceed, the additional study NCS of the lower limbs were

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performed. Other than the one patient who dropped out due to discomfort, all patients fully completed the study. No charges were placed for these additional study NCS, and patients were not compensated for undergoing them.

Quantifying the predictor variable (EDB bulk): Prior to performing the NCS, the lead investigator and a trainee independently assessed and graded the muscle bulk of the EDB using the following rating scale: Grade 1 = normal bulk, Grade 2 = diminished bulk, Grade 3 = severe atrophy. The muscle was inspected and palpated with the subject's foot relaxed, in multiple passively placed positions, and in maximally active toe extension. The position with the most prominent EDB visibility/palpability was used for grading. Normal bulk was defined as easily visualized and/or palpable muscle mass in any position. Diminished bulk was defined as muscle bulk that was present but difficult to observe or palpate. Severe atrophy was defined as no visual or palpable muscle mass. In order to calibrate assessments between the lead investigator and each trainee, the grading scale was reviewed in detail, and evaluation of EDB bulk was part of the usual exam performed on patients who were not included in the study. Unless excluded due to unilateral pitting edema or patient refusal, both feet from each participant were graded separately. Due to practical limitations, the grader was not blinded to the contralateral limb's rating. Trainees of the lead investigator (a resident or a fellow) independently evaluated the muscle bulk before the lead investigator entered the room. Due to changing rotation schedules, the same trainee could not be used for all subjects, and a total of 7 different trainees were used throughout the course of the study. Inter-rater reliability was calculated based on a comparison of the lead investigator with "generic trainee."

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Measurement of the Outcome Variable (fibular CMAP): Fibular motor NCS were performed as per American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) guidelines using standard technique with disposable electrodes. Due to practical limitations, it was not possible to achieve blinding of the investigator. Stimulation was performed over the deep fibular motor nerve at the anterior ankle, 9cm proximal to the recording site over the EDB muscle[8]. In order to ensure that the maximum response was obtained, the stimulus intensity and duration were incrementally increased, and the recording electrode was adjusted as necessary. When a response failed to reach the 4.0 mV threshold, multiple attempts were made to increase the stimulus intensity and duration and to optimize recording electrode placement to ensure that the measured amplitude truly was below the 4.0 mV threshold. If the measured supramaximal response was above the 4.0 mV threshold, the recording electrode was not always repositioned to evaluate for an even higher response since it was already above the threshold.

***Statistical Analysis*.**

Descriptive statistics are presented as frequencies and percentages for categorical variables and as means and either standard deviation or 95% confidence intervals (CIs) for continuous variables. Data distributions were assessed with histograms and quantile-quantile plots. Inter-rater reliability between the lead investigator and the (combined) trainees for assessing EDB bulk was calculated using the weighted Kappa statistic and 95% confidence interval. Additionally, inter-rater reliability of grading the muscle as normal (EDB bulk grade = 1) versus

abnormal (EDB bulk grade= 2 or 3) was assessed by calculating the simple kappa statistic and 95% confidence interval. Agreement was defined as almost perfect for kappa above 0.90, strong for 0.80 – 0.90, moderate for 0.60 – 0.79, weak for 0.40 – 0.59, minimal for 0.21 – 0.39, and none for 0 – 0.20[11]. All subsequent analyses were performed with the lead investigator's EDB bulk grade rating.

Relationships between EDB grade and CMAP amplitude (continuous) were first assessed via repeated measures generalized linear models (GLMs) with the subject treated as the repeated factor to account for the two feet being measured within each patient. When significant, post-hoc tests were conducted pairwise and adjusted for multiple comparisons with the Tukey-Kramer method. Subsequently, risk-adjusted GLMs were performed to determine whether EDB grade was associated with CMAP amplitude after adjusting for age, sex, BMI, peripheral neuropathy, and lumbar radiculopathy. Results from these models are presented as parameter estimates with 95% CIs.

The agreement between an EDB grade and CMAP amplitude being normal (≥ 4.0 mV) versus abnormal (< 4.0 mV) was assessed by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). All analyses were performed with SAS version 9.4 (Cary, NC, USA) with a two-sided level of significance of 0.05.

Results:

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A total of 102 feet from 52 patients (30 males, 22 females) were analyzed. The mean age of participants was 57.8 ± 16.7 (range 21.0 – 82.0) years, and the mean BMI was 26.1 ± 3.6 kg/m^2 (range: 18.8 – 35.6) kg/m^2 (Table 1). One patient had one foot excluded due to unilateral pitting edema, and another patient requested that the second foot not be evaluated due to discomfort from the NCS. All other patients fully completed the study.

All participants received a diagnosis based upon the clinical and electrodiagnostic findings for which they were originally referred to our clinic. Approximately half of the limbs showed no abnormalities. Abnormal findings included DSP (13%), lumbar radiculopathy (13%), carpal tunnel syndrome (10%), cervical radiculopathy (4%), ulnar mononeuropathy (4%), fibular mononeuropathy (2%), and DSP plus lumbar stenosis (2%) (Table 2). Inter-rater agreement of EDB bulk between the lead investigator and the combined trainees was weak, with a weighted kappa of 0.58 (0.45, 0.72). Agreement on rating EDB bulk as normal versus abnormal was moderate, with a kappa statistic of 0.65 (0.48, 0.72). The samples analyzed for the reliability calculations were the same samples used for the subsequent data calculations. All analyses below are based off of the data from the lead investigator.

72 feet (71%) were categorized as Grade 1 (normal bulk), 22 feet (22%) as Grade 2 (diminished bulk), and 8 feet (8%) as Grade 3 (atrophy). When considered alone, EDB grade was significantly related to CMAP amplitude ($p < 0.001$). The mean CMAP value was 5.9 ± 2.2 mV when muscle bulk was graded as normal, 3.4 ± 2.1 mV when graded as diminished, and 0.6 ± 0.9 mV when graded as severe atrophy (Figure 1). CMAP amplitude was lower for grade 2 than

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grade 1 ($p < 0.001$) and was even lower for grade 3 relative to grade 2 ($p < 0.001$ vs grade 2, and $p < 0.001$ vs grade 1). Increasing age was associated with greater EDB grade ($p = 0.002$) and lower CMAP amplitude ($p < 0.001$), as was increasing BMI ($p = 0.041$ vs EDB grade, 0.003 vs. CMAP amplitude). However, relationships with sex were not significant ($p = 0.398$ vs EDB grade, $p = 0.734$ vs CMAP amplitude). DSP was associated with greater EDB grade (DSP 60% grade 2 & 3, no DSP 24.1% grade 2 & 3, $p < 0.001$) and lower CMAP amplitude (DSP CMAP = 2.9 ± 1.8 mV, no DSP CMAP = 5.3 ± 2.6 mV; $p = 0.005$), as was lumbar radiculopathy (lumbar radiculopathy 53.9% EDB grade 2 & 3, no lumbar radiculopathy 25.8% EDB grade 2 & 3, $p = 0.006$; lumbar radiculopathy CMAP = 2.6 ± 2.3 mV, no lumbar radiculopathy CMAP = 5.2 ± 2.5 mV; $p < 0.001$). Interestingly, of the 9 patients diagnosed with an L5 radiculopathy, 7 were unilateral. In these patients, the fibular CMAP amplitude was lower on the symptomatic side (2.6 ± 2.4 mV) compared to the asymptomatic side (4.1 ± 1.8 mV).

After adjusting for DSP, lumbar radiculopathy, age, sex, and BMI, EDB grade was still significantly associated with CMAP amplitude ($p < 0.001$) (Table 3). After risk-adjustment, EDB grade 2 had a lower CMAP amplitude than grade 1 by 1.8 (0.9, 2.7) mV ($p < 0.001$). EDB grade 3 had a lower CMAP amplitude than grade 1 by 3.0 (1.9, 4.1) mV ($p < 0.001$). DSP was associated with a decrease of 1.2 (0.4, 2.1) mV in CMAP amplitude ($p = 0.015$), and lumbar radiculopathy was associated with a decrease of 1.6 (0.6, 2.7) mV in CMAP amplitude ($p = 0.019$). CMAP amplitude decreased by 0.5 (0.3, 0.8) mV for each 10 year increase in age ($p = 0.002$), while sex ($p = 0.432$) and BMI ($p = 0.728$) were not related to CMAP amplitude (Table 3).

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When looking at the ability for EDB grade to detect a CMAP amplitude as being normal (≥4.0 mV) versus abnormal (<4.0 mV), an EDB grade of 3 (atrophy) was a highly specific indicator that CMAP amplitude was abnormal (Table 4). All 8 patients (100%) with an EDB grade of 3 had an abnormal CMAP amplitude. While the specificity was high, the sensitivity of EDB graded as atrophy versus non-atrophy (grades 1 & 2 combined) as a metric was low, 0.29 (PPV = 1, NPV = 0.79). Conversely, looking at patients with normal EDB (grade 1), 64 (88.9%) of these patients were rated as normal by CMAP. Looking at a normal versus abnormal EDB (grades 2 & 3 combined) also had high specificity (0.86), and had better sensitivity (0.71) (PPV = .67, NPV = 0.89) as a diagnostic relative to grading as atrophied versus non-atrophied. These results taken together show that an EDB grading of 3 was a perfect indicator of patients having abnormal CMAP amplitude, while an EDB grading of normal was a strong indicator that patients' CMAP amplitude was normal. An EDB grade of 2 (diminished) provided inconclusive evidence regarding CMAP amplitude, as roughly half (45.5%) of these patients had normal CMAP amplitude and half (54.5%) had abnormal CMAP amplitude.

Summary of results:

In summary, EDB bulk grade was associated with fibular CMAP amplitude, and the clinical detection of fibular CMAP amplitude above or below the 4.0mV threshold based upon EDB muscle bulk was highly accurate in patients with normal muscle bulk and in those with severe atrophy.

Discussion:

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In this study, we demonstrated that the clinical evaluation of EDB muscle bulk can be measured reliably, and that this muscle bulk is associated with fibular CMAP amplitude. The mean CMAP amplitude of 0.6 ± 0.9 mV from severely atrophied EDB muscles was lower than that of EDB muscles with diminished bulk (3.4 ± 2.1 mV) and those with normal bulk (5.9 ± 2.2 mV), and the ability to detect CMAP amplitudes above or below the previously established clinically important value of 4.0 mV[8] was strong in patients with normal muscle bulk and in those with severe atrophy.

Previous work has shown that the 4.0 mV threshold is robustly associated with ankle proprioceptive thresholds, independent of age[8]. Since the ratio of hip strength to ankle proprioception is a predictor of unipedal stance time (frontal plane postural control)[12], falls[10], and injuries from falls[10], a simple method of detecting the fibular CMAP above or below 4.0 mV has clinical relevance. Other clinical tools have been shown to predict hip strength (lateral plank time) and ankle proprioceptive threshold (vibration sensation and monofilament testing)[13], and hence fall risk, yet none are as simple as the evaluation of EDB muscle bulk. Our study demonstrates that the mere evaluation of EDB bulk provides objective evidence for distal neuromuscular impairment. Perhaps most importantly, we showed that no patients with severe EDB atrophy had a fibular CMAP amplitude above the clinically relevant 4.0 mV threshold.

Limitations:

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Our study has limitations. First, the physician who obtained the fibular motor CMAP response was not blinded to the predictor variable (EDB bulk grade). As described in the methods section, in order to attempt to limit bias, great care was used to ensure accuracy of the measured CMAP amplitude above or below the 4.0 mV threshold. If bias did exist, it likely presented as an underestimate of the CMAP amplitude in those with a response above the 4.0 mV threshold, not for those below the 4.0 mV threshold. Therefore, our mean CMAP amplitude response in patients with normal EDB bulk may in fact be larger than the measured 5.9 mV, leading to an even greater difference in amplitude between those with normal vs abnormal EDB muscle bulk. Second, the inter-rater reliability analysis was performed by comparing the lead investigator with 7 different trainees. The learning curve required for each of the 7 trainees involved in the analysis, in addition to the relatively few feet scored as category 2 or 3, may have artificially lowered the weighted kappa and kappa statistics. A direct comparison of the same evaluators, ideally evaluators who were not trainees, would have been preferred. Unfortunately, logistics did not allow for this. Only the lead investigator's measurements were used in the analysis. Another limitation was that the original intent of our study was not to evaluate for a direct link of EDB muscle bulk with falls, but instead to make an indirect comparison by detecting low fibular CMAP amplitude. Lastly, anomalous tibial nerve innervation to the EDB muscle is known to occur[14,15]. Low amplitude fibular CMAP may be due to this anomalous innervation in some patients, yet our study protocol did not include routine evaluation of this finding in patients with low fibular CMAP amplitudes, thus potentially artificially decreasing the association between grade 1 muscle bulk and CMAP > 4.0 mV.

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Conclusions:

In conclusion, our study demonstrates the reliability of a simple clinical tool and its ability to accurately detect low fibular CMAP amplitude, a known surrogate for ankle proprioceptive precision and distal neuromuscular function. Further research is warranted to determine if EDB muscle bulk can predict patients at risk of falling.

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Table 1: Demographic information

Median Age (IQR)	57.8 (21.0 – 82.0)
Female/Male	42%/58%
BMI kg/m^2 (IQR)	26.1 (18.8 – 35.6)

IQR = interquartile range

BMI = body mass index

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Table 2: Frequency and percentage of limbs scoring EDB grades 1, 2, and 3 overall and by diagnosis*.

	Overall n (column %)	**EDB Grade 1: Normal** n (row %)	**EDB Grade 2: Diminished** n (row %)	**EDB Grade 3: Atrophy** n (row %)
Total	102 (100%)	72 (71%)	22 (22%)	8 (8%)
EMG Diagnosis				
Normal	54 (53%)	45 (83%)	9 (17%)	0 (0%)
Distal symmetric polyneuropathy	13 (13%)	4 (31%)	5 (39%)	4 (31%)
Lumbar radiculopathy (11/13 involved L5)	13 (13%)	6 (46%)	3 (23%)	4 (31%)
Carpal tunnel syndrome	10 (10%)	8 (80%)	2 (20%)	0 (0%)
Cervical radiculopathy	4 (4%)	4 (100%)	0 (0%)	0 (0%)
Ulnar mononeuropathy	4 (4%)	3 (75%)	1 (25%)	0 (0%)
Fibular mononeuropathy	2 (2%)	0 (0%)	2 (100%)	0 (0%)
Distal symmetric polyneuropathy & lumbar stenosis	2 (2%)	2 (100%)	0 (0%)	0 (0%)

* All diagnoses were determined based upon the clinical presentation and electrodiagnostic findings.

EDB = extensor digitorum brevis

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Table 3: Results of multivariable model for CMAP amplitude*.

Variable	Comparison	Parameter Estimate	95% Confidence Limits		p-value
EDB Bulk	2 vs 1	-1.83	-2.72	-0.94	**< 0.001***
	3 vs 1	-3.01	-4.08	-1.94	**< 0.001***
	3 vs 2	-1.18	-2.28	-0.08	0.091
Peripheral Neuropathy	Yes vs No	-1.23	-2.06	-0.41	**0.015***
Lumbar Radiculopathy	Yes vs No	-1.63	-2.69	-0.56	**0.002***
Sex	Female vs Male	-0.29	-1.02	0.43	0.432
Age	+ 1 year	-0.05	-0.08	-0.03	**0.002***
BMI	+ 1 point	0.02	-0.07	0.11	0.728

*Parameter estimates indicate the difference in CMAP amplitude for each categorical comparison or for a 1 unit increase for continuous variables.

CMAP = compound motor action potential

EDB = extensor digitorum brevis

BMI = body mass index

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Table 4. Rating of EDB grade versus CMAP amplitude falling above or below a CMAP amplitude of 4.0 mV.

		CMAP Amplitude	
		Abnormal (< 4.0 mV)	Normal (≥ 4 mV)
EDB Grade	Atrophy (3)	8 (28.6%)	0 (0.0%)
	Diminished (2)	12 (42.9%)	10 (13.5%)
	Normal (1)	8 (28.6%)	64 (86.5%)

EDB = extensor digitorum brevis

CMAP = compound motor action potential

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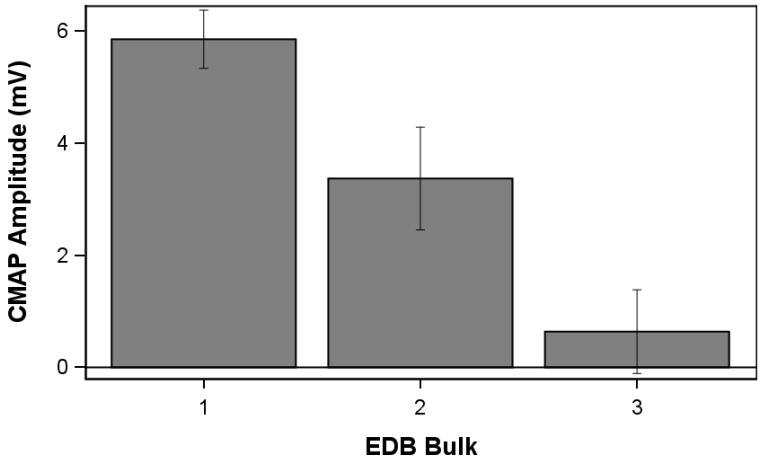
Figure 1:



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