J Appl Physiol 124: 696–703, 2018.
First published November 16, 2017; doi:10.1152/japplphysiol.00638.2017.

RESEARCH ARTICLE

Specific force of the vastus lateralis in adults with achondroplasia

David T. Sims, Gladys L. Onambélé-Pearson, Adrian Burden, Carl Payton, and Christopher I. Morse
Health, Exercise and Active Living Research, Manchester Metropolitan University, Cheshire, United Kingdom

Submitted 12 July 2017; accepted in final form 14 November 2017

Sims DT, Onambélé-Pearson GL, Burden A, Payton C, Morse CI. Specific force of the vastus lateralis in adults with achondroplasia. *J Appl Physiol* 124: 696–703, 2018. First published November 16, 2017; doi:10.1152/japplphysiol.00638.2017.—Achondroplasia is a clinical condition defined by shorter stature and disproportionate limb length. Force production in able-bodied individuals (controls) is proportional to muscle size, but given the disproportionate nature of achondroplasia, normalizing to anatomical cross-sectional area (ACSA) is inappropriate. The aim of this study was to assess specific force of the vastus lateralis (VL) in 10 adults with achondroplasia (22 ± 3 yr) and 18 sex-matched controls (22 ± 2 yr). Isometric torque (iMVCτ) of the dominant knee extensors (KE) and in vivo measures of VL muscle architecture, volume, activation, and patella tendon moment arm were used to calculate VL physiological CSA (PCSA), fascicle force, and specific force in both groups. Achondroplasic muscle volume was 53% smaller than controls (284 ± 36 vs. 604 ± 102 cm^3, $P < 0.001$). KE iMVCτ was 63% lower in achondroplasia compared with controls (95 ± 24 vs. 256 ± 47 N·m, $P < 0.001$). Activation and moment arm length were similar between groups ($P > 0.05$), but coactivation of bicep femoris of achondroplasic subjects was 70% more than controls (43 ± 20 vs. 13 ± 5%, $P < 0.001$). Achondroplasic subjects had 58% less PCSA (43 ± 10 vs. 74.7 ± 14 cm^2, $P < 0.001$), 29% lower fascicle force (702 ± 235 vs. 1704 ± 303 N, $P < 0.001$), and 29% lower specific force than control subjects (17 ± 6 vs. 24 ± 6 $N \cdot cm^{-2}$, $P = 0.012$). The smaller VL specific force in achondroplasia may be attributed to infiltration of fat and connective tissue, rather than to any difference in myofilament function.

NEW & NOTEWORTHY The novel observation of this study was the measurement of normalized force production in a group of individuals with disproportionate limb length-to-torso ratios.

achondroplasia; anatomical cross-sectional area; physiological cross-sectional area; specific force; vastus lateralis

INTRODUCTION

Achondroplasia is a condition characterized by disproportionate shorter limb length to stature, compared with age-matched average-sized individuals (18, 21, 39, 45). The contribution of force from the muscle in proportionally smaller groups has been investigated, with force production appearing to be proportional to muscle morphology, such as muscle volume and fascicle length (23, 37). With achondroplasia displaying disproportionate limb length and reduced whole body and segmental muscle mass, the muscle architecture and force production capacity may, in turn, be altered, but such observations have not been identified in achondroplasic populations.

Muscle morphology, defined here as muscle size and architecture, is a primary determinant of muscle function and can account for some of the differences observed in proportionally smaller people (6, 23, 24, 37, 43, 44, 49). Primarily, the determinants of muscle force are muscle shortening velocity, physiological cross-sectional area (PCSA) of the muscle, fascicle length, and muscle volume, respectively (38). Neural factors of the agonists and antagonists also contribute to force production, as well as the biomechanical form of the joint (29, 32, 34). In numerous clinical conditions, such as in aging and cerebral palsy, the prevalence of weakness corresponds with functional impairments, such as slower walking speeds and reduced performance of functional tasks (10, 22). In children with achondroplasia isometric knee extension, strength is less than age-matched controls (51); there is, however, no comparison of force production capacity in adults with achondroplasia, nor is there any measure of strength normalized for differences in muscle morphology or size.

The measurement of specific force integrates the measurement of muscle size, architecture, neural capacity and moment arm, providing a normalized value of force production (11, 50). Although there is some variability in specific force, the values are similar across different cohorts, muscles, and species (9, 11, 30, 37, 50). Although specific force is similar between muscle groups, such measurement in muscles of the leg, such as vastus lateralis (VL), is an indication of gait ability and oxygen uptake (52). Furthermore, recently, VL measurements of a large cohort of adult men have been published, which can be used as a reference data set (50). To our knowledge, there has been no measurement of force production in achondroplasic populations. Furthermore, to our knowledge, there appears to be no information on the adult achondroplasic population in relation to force production, other than a general assumption that muscle mass is lower in this group compared with age-matched average-sized people, hereafter referred to as "controls". Therefore, we chose to measure specific force to allow a comparison between achondroplasic and control subjects, which could differ in terms of neuromuscular, biomechanical, and architectural properties of the myotendinous unit.

Therefore, the aim of this study was to assess specific force in adult males with achondroplasia and to identify the neural, morphological, and biomechanical determinants of any difference in muscle force production between achondroplasic and control subjects.

Address for reprint requests and other correspondence: D. Sims, Dept. of Exercise and Sport Science, Manchester Metropolitan Univ., Cheshire CW1 5DU UK (e-mail: d.sims@mmu.ac.uk).

METHODS

Participants

After providing written informed consent, 28 participants volunteered to participate in the study. All were free from any lower limb injury 6 mo prior to data collection and self-reported good health using a physical activity readiness questionnaire [means (SD): 10 adult men with achondroplasia, age: 22 (3) yr, mass: 61.8 (8.5) kg, stature: 1.38 (0.05) m, body fat: 29.3 (2.9) % and 18 adult men, age: 22 (2) yr, mass: 78.3 (10.7) kg, stature: 1.79 (0.08) m, body fat: 22.4 (5.3) %]. Ethical approval was obtained by the local committee (Manchester Metropolitan University) and conformed to the declaration of Helsinki. Each participant attended one testing session at the laboratories of Manchester Metropolitan University where anthropometric, morphological, and force measurements of the knee extensors (KE) were carried out.

Whole Body Composition

Participants were asked to fast for ~8 h before body composition was assessed. A DEXA scanner (Hologic Discovery, Vertec Scientific, Reading, UK) was used to measure total body fat (%). A default whole body scan was selected for all trials; scans emitted dual-energy (140/100 kVp) fan-beam X-rays and lasted for ~7 min with each participant being exposed to ~8.4 μSv (5). The scanning region was 195 cm × 65 cm with 1.3 cm line spacing and a 0.2-cm point resolution.

Specific Force Calculation

Strength measurements. The torque derived from isometric maximal voluntary contraction (iMVCτ) of the dominant KE (achondroplasia: $n = 9$, right leg, control: $n = 16$, right leg) were recorded using an isokinetic dynamometer (Cybex Norm, Cybex International, Rosemont, IL). Participants were seated upright with the dynamometer and chair positioned in accordance with the calibration guidelines given by the manufacturer, so the lateral epicondyle was aligned with the dynamometer's central axis of rotation. Particularly, in the achondroplasia group, the chair and dynamometer were adjusted to align the lateral epicondyle, if needed; additional padding was placed behind the spine to help maintain a static knee angle throughout contractions. The participants' dominant leg was secured with Velcro straps to the chair on the distal portion of the thigh and to the dynamometer around the lower portion of the tibia (~80% tibia length), to maximize participants' comfort. All participants warmed up by performing six continuous submaximal concentric contractions (60°/s) of the KE and knee flexors (KF). Participants then completed a randomized trial of KE iMVCs at 10° intervals, between 60° and 100°, to anatomical zero (where 180° was anatomical zero). Because of the chair being repositioned in the achondroplasia group, joint angles were confirmed and recorded using a manual goniometer. Each participant received ~120 s rest between each trial. Throughout iMVC trials, participants were verbally encouraged to exert as much force as possible. Visual feedback was also provided to all participants on a monitor. KE and KF iMVCτ values were recorded (2,000 Hz) on a computer (Macintosh, iMac, Apple Computer, Cupertino, CA) via an A/D converter using an acquisition system (AcqKnowledge, Biopac Systems, Santa Barbara, CA). The angle that elicited peak KE iMVCτ was used for subsequent analysis.

Agonist Activation

Agonist activation of KE iMVCτ production is assessed to observed maximal activation of the muscle and is done so while participants are positioned in the isokinetic dynamometer. First, a counterweight was fixed to the dynamometer to minimize the compliance of the device. To measure agonist activation, two rubber stimulation pads (size ranging from 70 × 90 to 180 × 100 mm; Uni-Patch, Wabasha, MN) were placed proximally and distally along the transverse plane of the dominant femur. While in a relaxed state, a percutaneous electrical doublet stimulus (DS7, Digitimer stimulator, Welwyn, Garden City, UK) was passed through the KE at increased increments (~50 mV) and regular intervals (~20 s) until a plateau of twitch torque was measured. This supramaximal doublet stimulus was applied to the participants KE (interstimulus gap 10 μs and pulse width 50 μs) during KE iMVC. Doublet stimulus has been shown to improve the signal-to-noise ratio in the assessment of central activation (4, 27). A second doublet was applied ~5 s after the first stimulus when the muscles were fully relaxed, termed the potentiated doublet. Agonist activation was calculated using the following equation:

$$\text{Activation}\,(\%) = 100 \cdot \left[1 - \left(\frac{t - \text{iMVC}}{T}\right)\right]$$

where t is the interpolated doublet amplitude of the twitch torque, iMVCτ is the isometric maximal voluntary contraction torque, and T is the potentiated doublet amplitude (3).

Measurement of Coactivation

Coactivation of the KF was measured in all participants during a KE iMVC, and subsequent KF iMVCτ produced at the angle at which peak KE iMVCτ was measured. To determine coactivation of the KF, surface EMG was recorded over the biceps femoris (BF), as it is the largest of the KF group and is representative of the KF group as a whole (26). Furthermore, surface EMG was deemed adequate despite the adiposity levels in achondroplasia (17, 21, 42), as no differences in EMG readings are observed between groups of differing adiposity (8). Boundaries of the BF were determined using ultrasonography (Technos MXP Biosound Esaote) to ensure consistent placement of EMG electrodes over the KF. When established two pregelled, unipolar, 10-mm, Ag-AgCl percutaneous electromyography (EMG) electrodes (Ambu Neuroline 720, Baltorpbakken, Denmark) were placed distally at ~1/3 of muscle length, to avoid the motor unit of the BF, and ~2 mm apart along the midsagittal plane of the muscle (NORAXON, Scottsdale, AZ). A third electrode was placed on the lateral epicondyle of the same femur as a reference. Prior to the placement of the electrodes, areas of the skin were shaven, then cleaned using an alcoholic wipe to minimize skin impedance and, hence, improve the EMG signal. Raw EMG data were recorded at 2,000 Hz, with a high and low band-pass filter set at 10 and 500 Hz, respectively, and a notch set at 50 Hz. The integral of the root mean square was recorded 0.5 s either side of the KE and KF iMVCτ to quantify the level of KF muscle coactivation. On the basis of a linear relationship occurring between torque and EMG activity (32), KF torque during KE iMVC was derived by converting the percentage activation of KF EMG during KE iMVC to KF EMG during KF iMVC.

$$\text{KF}\tau = \left\{\frac{\left[\left(\text{KE} \div \text{KF}\right) \cdot 100\right]}{100}\right\} \cdot \text{KF iMVC}\tau$$

where KFτ is the KF torque during KE (N·m), KE is the agonist EMG (mV) recorded of the KE during KE iMVC, KF is the antagonist EMG (mV) recorded from the KE during KE iMVC, and KF iMVCτ is the torque (N·m) observed during KF iMVC.

The measurement of agonist and antagonist muscle activation is required for the accurate quantification of net KE iMVCτ production, both of which are used in the calculation of specific force (30, 50). Therefore, net KE iMVCτ was given as the sum of KE iMVCτ and KFτ, while a ratio of KF iMVCτ and KE iMVCτ was calculated to describe a balance of quadriceps to hamstring strength.

Measurement of Muscle Volume

To measure VL ACSA, B-mode ultrasonography (Technos MXP Biosound Esaote) was used to obtain a 50% muscle-length transverse

plane image of the VL (48). The origin and insertion of the dominant VL were marked, along with regular intervals of the medial and lateral edges. Muscle length (cm) was determined by the distance between the origin and insertion points with the 50th percentile marked on the skin. A wire mesh was secured to the skin using nonallergenic tape along the transverse plane. The wires were separated ~3 cm apart and ran sagittal to the muscle to act as echo-absorbing markers that projected a shadow on the ultrasound image to act as reference points for analysis (48). The 5-cm, 7.5-MHz linear array probe was placed transversely to the VL with ultrasound transmission gel across the skin. While the probe moved from the medial to the lateral border of the VL, an audio video interleave (AVI) recording with a sampling frequency of 25 Hz (Adobe Premiere Elements version 10, Adobe Systems) was taken. The field of view was set so that anatomical references (femur and aponeurosis between VL and vastus intermedius) were visible at all times. Measurements were taken while the participant was supine and at rest. Individual images (between 5 and 9), with at least two wire references, were extracted from the recording and used to reconstruct the muscle by overlapping the wire and aforementioned anatomical references, on photo editing software (Gimp, version 2.8.8, GNU Image Manipulation Program). Digitizing software (NIH ImageJ, version 1.44o, National Institutes of Health, Bethesda, MD) was used to measure the ACSA of the VL. The volume of the VL was calculated using previously reported constants of MRI regression (35), where

$$\text{VL volume} = \left(\frac{-2.9244}{4} + \frac{0.74}{3} + \frac{2.2178}{2} + 0.0244\right) \cdot \text{VL length} \cdot 50\%\ \text{ACSA}$$

Muscle Architecture

In vivo muscle architecture of the VL was conducted using B-mode ultrasonography (Technos MXP Biosound Esaote) during KE iMVC to observe fascicle length (cm) and pennation angle (θ). The 5-cm, 7.5-MHz linear array probe was held on the midsagittal plane on a previously established midpoint of the VL, measured equidistant from the origin-insertion and medial-lateral muscular borders. With water-soluble transmission gel, the probe was held against, and at a perpendicular angle to, the skin with minimal pressure. The depth of view was set to ensure a number of fasciculi insertion points and so that deep aponeurosis was in view (30). Ultrasound imaging and torque production were synchronized using an external square wave voltage trigger. Image recordings were in AVI format at a sample frequency of 25 Hz; single images were selected using capture software (Adobe Premiere Elements version 10, Adobe Systems). Images of the VL at rest and iMVC were analyzed using digitizing software (NIH ImageJ, version 1.44o, National Institutes of Health, Bethesda, MD), whereby fascicle length was determined as the length between the superficial and deep aponeuroses (38) and pennation angle was defined as the insertion angle of the fascicle into the deep aponeurosis (30). With the VL being one of the larger muscles in the body, invariably, the dimensions of the probe was not large enough to capture a full fascicle; for these cases, linear extrapolation was used to determine fascicle length, as little error (2–7%) is observed at the midpoint of the muscle (14, 15), again using digitizing software described above.

Physiological Cross-Sectional Area

The PCSA (in centimeters squared) was estimated as the ratio of VL muscle volume to fascicle length (30), assuming the model used to calculate muscle volume is cylindrical and that the muscle fibers are of constant length (48).

Moment Arm Length

A dual-energy X-ray absorptiometry (DEXA) scanning (Hologic Discovery, Vertec Scientific), in single energy mode (100 kVp), was used to obtain moment arm length of the patella tendon (PT_{MA}) (12). Participants were asked to lie on their side in a relaxed state. The dominant knee was positioned at the angle acquired from optimal peak force production using a manual goniometer. A single-array sagittal plane scan was taken of the knee using a 22.3 × 13.7 cm field of view. Obtained scans were exported to and analyzed on a Dicom viewer (OsiriZ 5.0.2, Pixmeo Sarl, Geneva, Switzerland). Moment arm length (in meters) was determined as the perpendicular distance between the estimated tibiofemoral contact point and the posterior aspect of the patella tendon (57).

Fascicle Force and Specific Force

To estimate VL fascicle force and, in turn, specific force, the following steps were used.

Patella tendon force (*N*) was calculated using the following equation (41):

$$F_{PT} = \frac{\text{Net KE MVC}\tau}{\text{MA}}$$

where F_{PT} is the force at the patella tendon (in newtons) during KE iMVC, net KE iMVCτ is calculated above, and MA is the length of the moment arm (in meters).

Previously reported data show the relative contribution of the VL to the patella tendon to be around 22% (38). This calculation was then used to calculate VL fascicle force by expressing the VL fascicle force as a ratio of the VL contribution to the cosine of the pennation angle (radians) at KE iMVC.

$$\text{Fascicle Force} = \frac{VL_{con}}{\cos\theta}$$

where VL_{con} is the VL contribution (in newtons) and cosθ is the cosine of pennation at iMVC (in radians). Specific force was represented as the ratio between VL fascicle force and VL PCSA.

Statistical Analysis

All data were collated onto a personal computer (Macintosh, MacBook Pro, Apple Computer, Cupertino, CA) and analyzed using SPSS (version 22.0, IBM). Data were assumed parametric following Shapiro-Wilk and Levene's tests. Independent *t*-tests were carried out on most measured variables. In addition, Pearson's correlations were performed between related dependent variables. For variables that violated parametric assumptions, a Levene's adjusted *P* value or a Mann-Whitney *U* (denoted by * and †, respectively, in Tables 1 and 2) was performed. Study power was assessed using G*Power and was found to be above 0.8, and α was set at ≤0.05. All results are reported as means (SD).

RESULTS

Achondroplasic subjects were 23% smaller in stature ($P < 0.001$), 19% lighter in body mass ($P < 0.001$) and had 24% more body fat ($P < 0.001$) than controls. There was no difference in age between groups ($P = 0.487$).

KE and KF iMVCτ

Adult men with achondroplasia produced 63% less KE iMVCτ than controls (Table 1). KF iMVCτ was also significantly different (Table 1), again with achondroplasic subjects producing 82% less KE iMVCτ than controls. When expressed as a ratio between absolute KE iMVCτ and KF iMVCτ, achondroplasia produced 49% more iMVCτ from the KE compared with KF than controls (Table 2).

Table 1. *Morphological and functional characteristics of the vastus lateralis in controls and achondroplasic adults*

	Control	Achondroplasia	*P* Value
iMVCτ KE, N·m	256 (47)	95 (24)	<0.001
iMVCτ KF, N·m*	105 (19)	19 (7)	<0.01
Activation, % *	92.0 (5.9)	83.9 (13.9)	0.105
Coactivation, % *	12.6 (5.3)	42.6 (20)	0.001
Net iMVCτ, N·m†	287 (49)	106 (26)	<0.001
Volume, cm^3*	604 (102)	284 (36)	<0.001
Fascicle length, cm*	8.2 (1.5)	6.8 (1.5)	0.027
ACSA, cm^2*	27.7 (4.4)	22.2 (2.6)	<0.001
Pennation angle, †	17.4 (2.4)	20.9 (4.6)	0.027
Muscle thickness, cm	28.4 (7.6)	20.6 (8.3)	0.550
PCSA, cm^2	74.7 (13.7)	43.2 (9.9)	<0.001
Moment arm, m†	0.040 (0.002)	0.037 (0.005)	0.309
Patella tendon force, N	7296 (1319)	2930 (974)	<0.001
VL fascicle force, N	1704 (303)	702 (235)	<0.001
Specific force, $N \cdot cm^{-2}$†	23.6 (6.4)	16.7 (6.0)	0.014

Values are presented as means (SD). iMVCτ, isometric maximal voluntary contraction torque; ACSA, anatomical cross-sectional area; PCSA, physiological cross-sectional area. *Adjusted *P* value following Levene's. †Mann Whitney-*U* test.

Activation and Coactivation

There was no difference in maximal activation between achondroplasic and control participants; however, achondroplasia had a 70% greater coactivation of the BF during KE iMVC compared with controls (Table 1).

Net KE iMVCτ

Paired samples *t*-test revealed that both groups significantly increased KE iMVC when corrected for BF coactivation, with achondroplasia increasing by 7% and controls by 5%, respectively (Table 1). The net KE iMVCτ produced by the VL was 63% less in achondroplasia compared with controls (Table 1). There was no significant correlation between body fat percentage and net KE iMVCτ in achondroplasia ($r = 0.110$, $P = 0.763$) or controls ($r = 0.411$, $P = 0.090$).

Morphology and Architecture

Achondroplasic subjects had 41% smaller VL length than controls (Table 1). VL morphology differed between groups, with the achondroplasia group having a 20% smaller ACSA than the control group (Table 1, Fig. 1) and, in turn, a 53% smaller muscle volume than controls (Table 1). Achondroplasia exhibited a 17% greater pennation angle (Table 1) but 17% smaller fascicle length (Table 1) during KE iMVC. PCSA was found to be 42% smaller in achondroplasic than control adults (Table 1). Correlations revealed no significant relationship between VL muscle volume and net KE iMVCτ production in achondroplasia ($R^2 = 0.056$, $P = 0.508$, Fig. 2), whereas for the same variables in controls, a significant relationship did exist ($R^2 = 0.286$, $P = 0.022$, Fig. 2). Despite the diverging regression lines, a *z*-transformation showed the slopes were similar ($P = 0.442$).

Presenting KE iMVCτ as a ratio to ACSA, achondroplasia produce 53% less force per unit area compared with controls (Table 2). When net KE iMVCτ is expressed as a ratio with total body mass, achondroplasia again display a 43% reduction to controls (Table 2). Achondroplasia displayed a 67% reduction in net KE iMVCτ when presented as a ratio to LBM (Table 2). There was no relationship between ACSA and PCSA ($R^2 = 0.016$, $P > 0.05$) for achondroplasia, whereas a significant relationship for the same variables was observed for controls ($R^2 = 0.254$, $P = 0.032$).

Force Measurements

The length of the PT_{MA} was similar between achondroplasia and controls (Table 1). All force measurements were statistically lower in achondroplasia compared with controls with patella tendon force, fascicle force, and specific force being 60, 59, and 29% lower, respectively (Table 1).

DISCUSSION

Here, we aimed to assess the in vivo muscle morphology, KE iMVCτ production, and specific force of the VL in adults with achondroplasia and age- and sex-matched healthy adults. The main findings were *1*) net KE iMVCτ, VL ACSA, volume and PCSA were smaller in achondroplasia than controls, *2*) differences in net KE iMVCτ were not accounted for by the differences in muscle size, *3*) KF coactivation was higher in achondroplasia than controls, and *4*) when morphological, architectural, neurological, and biomechanical differences were accounted for, a 29% smaller specific force was observed in achondroplasia.

A large portion of neuromuscular function research describes the relationship between muscle size and force production, suggesting that muscle size is the predetermining factor for muscle strength (7, 33, 50, 54). Groups of shorter statures consistently present with smaller muscle size and lower MVC strength than their taller counterparts (6, 23, 37, 43, 49); when iMVCτ is normalized to muscle size, differences between control and short stature groups are nullified (6, 23, 49). The data from the present study are partially consistent with these previous findings. Subjects with achondroplasia were 82% weaker than controls in terms of KE iMVCτ; however, this was not entirely accounted for by ACSA, which was only 20% smaller. Therefore, it is likely that architectural and neurological factors contribute to weakness in achondroplasia. It should be noted, however, that despite accounting for these factors, a deficit in achondroplasia-specific force remains, which could be subsequently attributed to physiological factors between

Table 2. *Morphological and functional characteristics of the vastus lateralis normalized anatomical structures in controls and achondroplasic adults*

	Control	Achondroplasia	*P* Value
iMVCτ KE:KF, %	41.1 (9.2)	20.2 (6.7)	<0.001
VL Length:Stature, %†	18.8 (0.8)	14.3 (0.7)	<0.001
TBM:Volume, kg/cm^{-3}	7.76 (1.17)	4.65 (0.69)	<0.001
Net iMVCτ:ASCA, $N \cdot m \cdot cm^{-2}$	2.14 (0.37)	2.81 (0.73)	0.003
Net iMVCτ:TBM, $N \cdot m \cdot kg^{-1}$	3.72 (0.71)	1.71 (0.28)	<0.001
Net iMVCτ:LBM, $N \cdot m \cdot kg^{-1}$†	4.99 (0.78)	2.54 (0.43)	<0.001
Net iMVCτ:Volume, $N \cdot m \cdot cm^{-3}$	0.48 (0.08)	0.38 (0.10)	0.006
PT Moment arm:VL Length, cm†	11.78 (0.96)	19.07 (3.25)	<0.001
Net iMVCτ:PSCA, $N \cdot m \cdot cm^{-2}$	3.96 (0.99)	2.55 (0.80)	0.001

Values are presented as means (SD).VL, vastus lateralis; TBM, Total body mass; iMVCτ, isometric maximal voluntary contraction torque; ACSA, anatomical cross-sectional area; PCSA, physiological cross-sectional area; PT, patella tendon. †Mann-Whitney *U*-test.

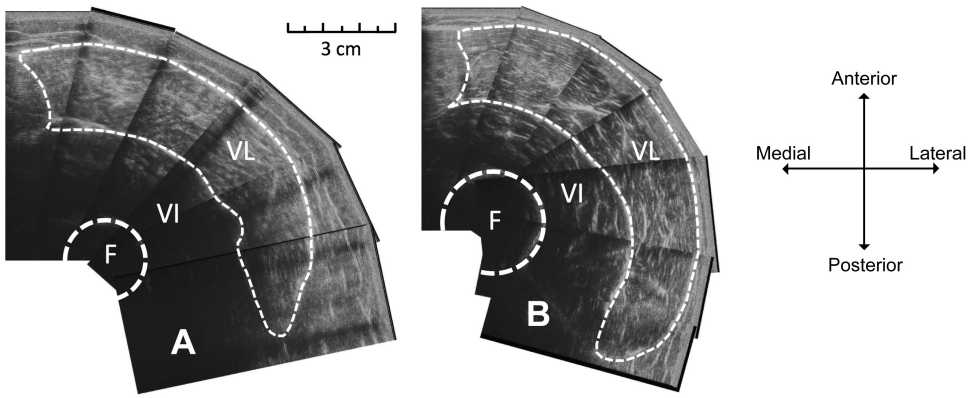

Fig. 1. 50% ACSA of an achondroplasia adult (*A*) and a healthy adult (*B*). VL, vastus lateralis; VI, vastus intermedius; F, femur.

groups or methodological measures of specific force, as discussed below.

Muscle Morphology in Achondroplasia

The extent of group differences in muscle size between achondroplasia and controls was not consistent for each variable. For example, a 20% smaller VL ACSA in achondroplasia underestimated the difference in PCSA, which was 42% smaller than controls. This was due to the smaller muscle length and, hence, smaller VL volume in achondroplasia compared with controls. Therefore, ACSA must be considered an inaccurate method of assessing contractile area between groups of heterogeneous muscle length, such as presented here.

Although PCSA is the closest approximation to sarcomeres in parallel and, therefore, contractile area (28), it is possible that PCSA may be overestimated in the achondroplasic group. The overestimation of PCSA in achondroplasia is likely due to the differences in architectural properties at iMVC between groups. In controls, increased tendon compliance (i.e., more strain when under a relative force) alters muscle architecture at iMVC, with increased pennation angle, fiber shortening, and a leftward shift in the length tension relationship observed (30, 46, 47). Here, only increased pennation angle between groups was observed as resting fiber length was not measured. Assuming the achondroplasic patella tendon is more compliant than controls, given the observations made here, achondroplasic fiber length is likely to be shorter at iMVC than it would be were the patella tendon compliance the same between groups. PCSA is, therefore, overestimated as PCSA = ACSA/fiber length. Given that PCSA is the denominator when calculating specific force, a large PCSA (with the same fascicle force) equates to a lower specific force. For example, in the present study, achondroplasia fiber length was 17% shorter and 17% more pennate at iMVC than controls. If the fiber angle were to remain the same between groups at KE iMVC, fiber length of achondroplasia would be 9% longer than the presented values and result in a 47% smaller PCSA compared with controls, 5% more than the measured values. This consequently leads to a 15% smaller achondroplasia-specific force compared with controls. Therefore, the differences in muscle architecture at iMVC between groups appear to contribute to the difference in specific force and could be partly due to a more compliant achondroplasia patella tendon. However, there appears to be no measure of achondroplasic tendon compliance within the literature to confirm this. Furthermore, this theory may only explain some of the 23% difference in specific force between groups.

Specific Force

Specific force provides an accurate representation of the in vivo contractile properties of the whole muscle and has been used to describe the force characteristics of numerous different cohorts and muscle groups (9, 11, 15, 30, 36–38, 43, 50). Recently, it has been shown that interindividual variability in

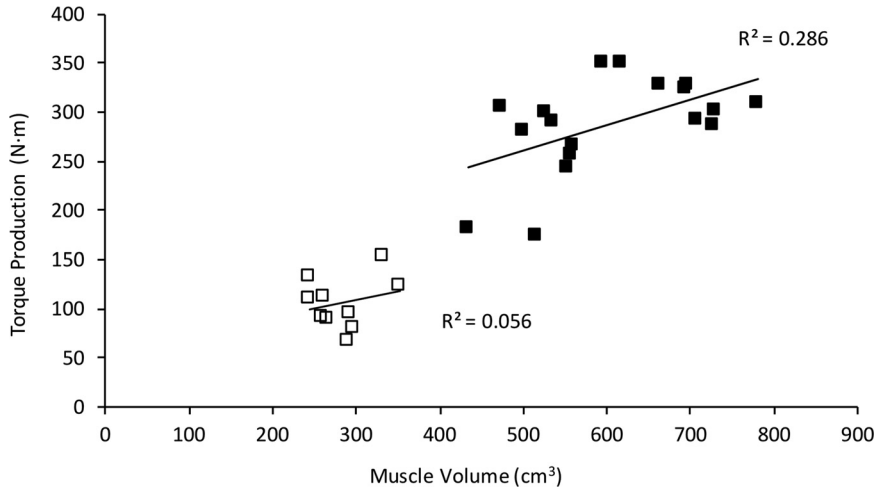

Fig. 2. Scatterplot showing the relationship between VL muscle volume (cm^3) and torque production (N·m) for achondroplasia (□) and control subjects (■). Trend lines including R^2 are also given for each group, respectively.

the measurements of specific force alludes to the fact that population variance in specific force may be due to a lower fiber-specific force (i.e., myofilament differences), or an overestimation of muscle area through the inclusion of noncontractile material in the measurement of muscle mass (50). Several research groups have investigated specific force production at the myofilament level to identify intramuscular differences (55, 56, 58). In the present study, specific force was measured at the fascicle level, with no apparent measure of force production made at the myofilament level in achondroplasia. It could be suggested though, that as achondroplasia is determined by a collagenous defect during development (18, 20), the protein structures at the myofilament level may be different than controls, which may contribute to the lower achondroplasia-specific force presented.

It is possible that the presentation of a lower specific force could be due, in part, to an overestimation of muscle size owing to the use of ultrasound to measure ACSA. Ultrasound, as with MRI, requires the measurement of the area encapsulated by aponeuroses to determine ACSA. The area within these limits includes muscle, connective tissue, and fat infiltration. Previous reports (16, 17, 42) and this study show that achondroplasic individuals have increased body fat percentage. The fibroblast mutation that causes achondroplasia may also play some part in connective tissue distribution within the muscle, although this is at present unreported. Therefore, the measured achondroplasic ACSA may reflect a "pseudo-hypertrophy" due to the probable increase of intramuscular fat infiltration, as observed in people with increased body fat (53). This pseudohypertrophy would increase muscle volume and PCSA measurement, with no change in contractile mass and, in turn, reduce the calculation of achondroplasia-specific force; it is important to note here that this methodological limitation is not only present in achondroplasia. Regardless of these methodological discrepancies, when scaling strength and muscle size, a lower specific force persists in the present achondroplasia participants, which could be attributed to either an infiltration of noncontractile material, differences in single fiber properties, or differences in tendon properties.

Coactivation and Moment Arm Length

In this study, the use of DEXA to measure PT_{MA} led to two important observations of the achondroplasic knee. First, there appears to be a lower joint congruency between femur and tibia in the achondroplasic knee (Fig. 3), agreeing with observations by Aykol et al. (1). The apparent reduced tibiofemoral joint congruency in achondroplasia would likely reduce tibiofemoral joint stability. In clinical, injured, and juvenile populations, where joint congruency is reduced, increased coactivation of the BF is observed during KE (13, 25, 26). In the present study, achondroplasia had a 70% increased coactivation of the BF during KE iMVC compared with controls. Therefore, the increased coactivation of achondroplasic BF during KE iMVC is likely due to the reduced tibiofemoral joint congruency. Furthermore, the increased coactivation of the achondroplasic BF may act as an injury prevention mechanism. In this case, achondroplasic hamstrings are activating during KE to reduce the anterior movement of the tibia in relation to the femur. This would protect ligamentous structures in the knee, such as the anterior cruciate ligament. It is probable that this mechanism exists in other achondroplasic muscle groups and joints, as well as the knee. The increased coactivation of hamstrings, and other muscles, may also influence activities of daily living, such as walking economy. There is, however, a lack of comparative data expressing the activation profiles of achondroplasic muscle during contraction to expand on the theories presented. Therefore, the suggestions made from the current findings warrant further work.

The second observation from DEXA scanning of the achondroplasic knee was that absolute PT_{MA} between groups was the same, meaning that achondroplasia has a longer PT_{MA} relative to the femur (here measured as VL length). This finding is different to other shorter-stature groups that show a proportionally smaller moment arms compared with taller-stature individuals (37). The relatively larger PT_{MA} in achondroplasia subjects is likely to aid KE torque production, despite the 63% lower net KE iMVCτ compared with controls. For example, were the PT_{MA} of the current achondroplasic population to be

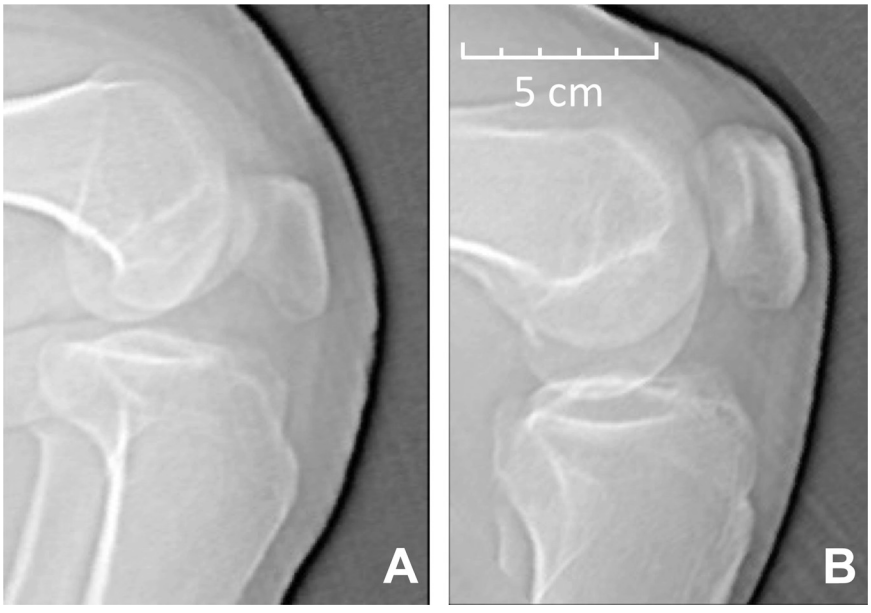

Fig. 3. Sagittal knee scans of one achondroplasic (*A*) and one control (*B*) subject showing the reduced femoral contact point with the tibia in achondroplasia.

proportionally smaller to their femur length (i.e., 37% shorter), the achondroplasia group would have produced 76% less net KE iMVCτ than the control group. Although PT_{MA} appears to aid achondroplasic torque production, PT_{MA} changes during KE (2, 31, 32), which leads to differences in force production (57). In the present study, we measured PT_{MA} at rest and did not account for changes of PT_{MA} during contraction. We assumed that the changes in PT_{MA} during KE iMVC would be similar between groups, as it has not been reported whether achondroplasic PT_{MA} changes in a similar fashion to control's PT_{MA} during KE. Any change in achondroplasic PT_{MA} during contraction may further aid or hinder achondroplasic torque production, but this has yet to be observed. The presented data from this study appear to be the only data that account for achondroplasic moment arm during contraction in any joint.

Clinical Implications

The present observations of a lower specific force, higher body fat, shorter stature, and lower muscle volume in achondroplasia, could contribute to those with achondroplasia, requiring a greater relative force production to complete activities of daily living compared with controls, such as walking. During walking, the lower muscle volume and higher body mass of achondroplasic individuals would likely increase the required force production per step to maintain locomotion. This increased force production may, in turn, increase achondroplasic walking economy. Furthermore, the decrease in achondroplasic KE and KF iMVCτ, higher hamstring coactivation, and lower specific force would suggest achondroplasic subjects may be at greater risk of falls and reduced postural stability compared with controls, as has been observed in control groups (40). Therefore, addressing interventions that aim to increase the absolute force production of achondroplasic muscle would likely increase these subjects' quality of life by aiding walking economy, reducing the risk of falling, and reducing injury risk.

Conclusion

To our knowledge, this is the first study to systematically account for various physiological and biomechanical modulators of force production in muscles of achondroplasia. The main finding is that achondroplasia subjects produce 23% less specific force than controls. These results may only explain the variance in muscle morphology, as further work is needed to explore methodological and myofilament differences within achondroplasia-specific force to increase the validity of these data.

GRANTS

The authors thank the Dwarf Sports Association (Dronfield, UK, registered charity number 1041961) for assistance in recruitment and Dream it Believe it Achieve it (Northwich, UK, registered charity number 1153116) for which D. Sims received initial postgraduate funding.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.T.S., G.L.O.-P., A.B., C.P., and C.I.M. conceived and designed research; D.T.S. performed experiments; D.T.S. and C.I.M. analyzed data; D.T.S., G.L.O.-P., A.B., C.P., and C.I.M. interpreted results of experiments; D.T.S. prepared figures; D.T.S. drafted manuscript; D.T.S., G.L.O.-P., A.B., C.P., and C.I.M. edited and revised manuscript; D.T.S., G.L.O.-P., A.B., C.P., and C.I.M. approved final version of manuscript.

REFERENCES

1. **Akyol Y, Averill LW, Atanda A, Kecskemethy HH, Bober MB, Mackenzie WG.** Magnetic resonance evaluation of the knee in children and adolescents with achondroplasia. *Pediatr Radiol* 45: 888–895, 2015. doi:10.1007/s00247-014-3228-1.
2. **Baltzopoulos V.** A videofluoroscopy method for optical distortion correction and measurement of knee-joint kinematics. *Clin Biomech (Bristol, Avon)* 10: 85–92, 1995. doi:10.1016/0268-0033(95)92044-M.
3. **Behm D, Power K, Drinkwater E.** Comparison of interpolation and central activation ratios as measures of muscle inactivation. *Muscle Nerve* 24: 925–934, 2001. doi:10.1002/mus.1090.
4. **Belanger AY, McComas AJ.** Extent of motor unit activation during effort. *J Appl Physiol Respir Environ Exerc Physiol* 51: 1131–1135, 1981.
5. **Blake GM, Naeem M, Boutros M.** Comparison of effective dose to children and adults from dual X-ray absorptiometry examinations. *Bone* 38: 935–942, 2006. doi:10.1016/j.bone.2005.11.007.
6. **Bottinelli R, Narici M, Pellegrino MA, Kayser B, Canepari M, Faglia G, Sartorio A.** Contractile properties and fiber type distribution of quadriceps muscles in adults with childhood-onset growth hormone deficiency. *J Clin Endocrinol Metab* 82: 4133–4138, 1997. doi:10.1210/jcem.82.12.4426.
7. **Bruce SA, Phillips SK, Woledge RC.** Interpreting the relation between force and cross-sectional area in human muscle. *Med Sci Sports Exerc* 29: 677–683, 1997. doi:10.1097/00005768-199705000-00014.
8. **De Vito G, McHugh D, Macaluso A, Riches PE.** Is the coactivation of biceps femoris during isometric knee extension affected by adiposity in healthy young humans? *J Electromyogr Kinesiol* 13: 425–431, 2003. doi:10.1016/S1050-6411(03)00061-0.
9. **Degens H, Hoofd L, Binkhorst RA.** Specific force of the rat plantaris muscle changes with age, but not with overload. *Mech Ageing Dev* 78: 215–219, 1995. doi:10.1016/0047-6374(94)01538-W.
10. **Dodd KJ, Taylor NF, Damiano DL.** A systematic review of the effectiveness of strength-training programs for people with cerebral palsy. *Arch Phys Med Rehabil* 83: 1157–1164, 2002. doi:10.1053/apmr.2002.34286.
11. **Erskine RM, Jones DA, Maganaris CN, Degens H.** *In vivo* specific tension of the human quadriceps femoris muscle. *Eur J Appl Physiol* 106: 827–838, 2009. doi:10.1007/s00421-009-1085-7.
12. **Erskine RM, Morse CI, Day SH, Williams AG, Onambele-Pearson GL.** The human patellar tendon moment arm assessed in vivo using dual-energy X-ray absorptiometry. *J Biomech* 47: 1294–1298, 2014. doi:10.1016/j.jbiomech.2014.02.016.
13. **Fairbank JC, Pynsent PB, van Poortvliet JA, Phillips H.** Mechanical factors in the incidence of knee pain in adolescents and young adults. *J Bone Joint Surg Br* 66: 685–693, 1984.
14. **Finni T, Ikegawa S, Lepola V, Komi PV.** Comparison of force-velocity relationships of vastus lateralis muscle in isokinetic and in stretch-shortening cycle exercises. *Acta Physiol Scand* 177: 483–491, 2003. doi:10.1046/j.1365-201X.2003.01069.x.
15. **Fukunaga T, Roy RR, Shellock FG, Hodgson JA, Edgerton VR.** Specific tension of human plantar flexors and dorsiflexors. *J Appl Physiol (1985)* 80: 158–165, 1996. doi:10.1152/jappl.1996.80.1.158.
16. **Hecht JT, Hood OJ, Schwartz RJ, Hennessey JC, Bernhardt BA, Horton WA, Opitz JM, Reynolds JF.** Obesity in achondroplasia. *Am J Med Genet* 31: 597–602, 1988. doi:10.1002/ajmg.1320310314.
17. **Hoover-Fong JE, McGready J, Schulze KJ, Barnes H, Scott CI.** Weight for age charts for children with achondroplasia. *Am J Med Genet A* 143A: 2227–2235, 2007. doi:10.1002/ajmg.a.31873.
18. **Horton WA, Hall JG, Hecht JT.** Achondroplasia. *Lancet* 370: 162–172, 2007. doi:10.1016/S0140-6736(07)61090-3.
19. **Horton WA, Lunstrum GP.** Fibroblast growth factor receptor 3 mutations in achondroplasia and related forms of dwarfism. *Rev Endocr Metab Disord* 3: 381–385, 2002. doi:10.1023/A:1020914026829.
20. **Hunter AG, Hecht JT, Scott CI Jr.** Standard weight for height curves in achondroplasia. *Am J Med Genet* 62: 255–261, 1996. doi:10.1002/(SICI)1096-8628(19960329)62:3<255::AID-AJMG10>3.0.CO;2-J.
21. **Hurley MV, Rees J, Newham DJ.** Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects. *Age Ageing* 27: 55–62, 1998. doi:10.1093/ageing/27.1.55.
22. **Janssen YJH, Doornbos J, Roelfsema F.** Changes in muscle volume, strength, and bioenergetics during recombinant human growth hormone

(GH) therapy in adults with GH deficiency. *J Clin Endocrinol Metab* 84: 279–284, 1999.
24. **Kanehisa H, Ikegawa S, Tsunoda N, Fukunaga T.** Strength and cross-sectional area of knee extensor muscles in children. *Eur J Appl Physiol Occup Physiol* 68: 402–405, 1994. doi:10.1007/BF00843736.
25. **Kellis E.** Antagonist moment of force during maximal knee extension in pubertal boys: effects of quadriceps fatigue. *Eur J Appl Physiol* 89: 271–280, 2003. doi:10.1007/s00421-003-0795-5.
26. **Kellis E, Unnithan VB.** Co-activation of vastus lateralis and biceps femoris muscles in pubertal children and adults. *Eur J Appl Physiol Occup Physiol* 79: 504–511, 1999. doi:10.1007/s004210050545.
27. **Kent-Braun JA, Ng AV.** Specific strength and voluntary muscle activation in young and elderly women and men. *J Appl Physiol (1985)* 87: 22–29, 1999. doi:10.1152/jappl.1999.87.1.22.
28. **Lieber RL, Fridén J.** Functional and clinical significance of skeletal muscle architecture. *Muscle Nerve* 23: 1647–1666, 2000. doi:10.1002/1097-4598(200011)23:11<1647::AID-MUS1>3.0.CO;2-M.
29. **Maganaris CN.** Force-length characteristics of in vivo human skeletal muscle. *Acta Physiol Scand* 172: 279–285, 2001. doi:10.1046/j.1365-201x.2001.00799.x.
30. **Maganaris CN, Baltzopoulos V, Ball D, Sargeant AJ.** In vivo specific tension of human skeletal muscle. *J Appl Physiol (1985)* 90: 865–872, 2001. doi:10.1152/jappl.2001.90.3.865.
31. **Maganaris CN, Baltzopoulos V, Sargeant AJ.** Changes in the tibialis anterior tendon moment arm from rest to maximum isometric dorsiflexion: in vivo observations in man. *Clin Biomech (Bristol, Avon)* 14: 661–666, 1999. doi:10.1016/S0268-0033(99)00018-2.
32. **Maganaris CN, Baltzopoulos V, Sargeant AJ.** Differences in human antagonistic ankle dorsiflexor coactivation between legs; can they explain the moment deficit in the weaker plantarflexor leg? *Exp Physiol* 83: 843–855, 1998. doi:10.1113/expphysiol.1998.sp004164.
33. **Maughan RJ, Watson JS, Weir J.** Strength and cross-sectional area of human skeletal muscle. *J Physiol* 338: 37–49, 1983. doi:10.1113/jphysiol.1983.sp014658.
34. **Merton PA.** Voluntary strength and fatigue. *J Physiol* 123: 553–564, 1954. doi:10.1113/jphysiol.1954.sp005070.
35. **Morse CI, Degens H, Jones DA.** The validity of estimating quadriceps volume from single MRI cross-sections in young men. *Eur J Appl Physiol* 100: 267–274, 2007. doi:10.1007/s00421-007-0429-4.
36. **Morse CI, Thom JM, Mian OS, Birch KM, Narici MV.** Gastrocnemius specific force is increased in elderly males following a 12-month physical training programme. *Eur J Appl Physiol* 100: 563–570, 2007. doi:10.1007/s00421-006-0246-1.
37. **Morse CI, Tolfrey K, Thom JM, Vassilopoulos V, Maganaris CN, Narici MV.** Gastrocnemius muscle specific force in boys and men. *J Appl Physiol (1985)* 104: 469–474, 2008. doi:10.1152/japplphysiol.00697.2007.
38. **Narici MV, Landoni L, Minetti AE.** Assessment of human knee extensor muscles stress from *in vivo* physiological cross-sectional area and strength measurements. *Eur J Appl Physiol Occup Physiol* 65: 438–444, 1992. doi:10.1007/BF00243511.
39. **Nehme A-M, Riseborough EJ, Tredwell SJ.** Skeletal growth and development of the achondroplastic dwarf. *Clin Orthop Relat Res* (116): 8–23, 1976.
40. **Onambélé GL, Narici MV, Maganaris CN.** Calf muscle-tendon properties and postural balance in old age. *J Appl Physiol (1985)* 100: 2048–2056, 2006. doi:10.1152/japplphysiol.01442.2005.
41. **Onambélé GN, Burgess K, Pearson SJ.** Gender-specific *in vivo* measurement of the structural and mechanical properties of the human patellar tendon. *J Orthop Res* 25: 1635–1642, 2007. doi:10.1002/jor.20404.
42. **Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Knerr AN, Kendrick ZV, Kavle EC, Donohoe M, Tappy L, Boden G.** Resting metabolic rate and body composition of achondroplastic dwarfs. *Medicine (Baltimore)* 69: 56–67, 1990. doi:10.1097/00005792-199001000-00005.
43. **O'Brien TD, Reeves ND, Baltzopoulos V, Jones DA, Maganaris CN.** *In vivo* measurements of muscle-specific tension in adults and children. *Exp Physiol* 95: 202–210, 2010. doi:10.1113/expphysiol.2009.048967.
44. **O'Brien TD, Reeves ND, Baltzopoulos V, Jones DA, Maganaris CN.** Muscle-tendon structure and dimensions in adults and children. *J Anat* 216: 631–642, 2010. doi:10.1111/j.1469-7580.2010.01218.x.
45. **Ponseti IV.** Skeletal growth in achondroplasia. *J Bone Joint Surg Am* 52: 701–716, 1970. doi:10.2106/00004623-197052040-00004.
46. **Reeves ND.** Adaptation of the tendon to mechanical usage. *J Musculoskelet Neuronal Interact* 6: 174–180, 2006.
47. **Reeves ND, Maganaris CN, Narici MV.** Effect of strength training on human patella tendon mechanical properties of older individuals. *J Physiol* 548: 971–981, 2003. doi:10.1113/jphysiol.2002.035576.
48. **Reeves ND, Maganaris CN, Narici MV.** Ultrasonographic assessment of human skeletal muscle size. *Eur J Appl Physiol* 91: 116–118, 2004. doi:10.1007/s00421-003-0961-9.
49. **Sartorio A, Narici MV.** Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. *Clin Physiol* 14: 527–537, 1994. doi:10.1111/j.1475-097X.1994.tb00411.x.
50. **Stebbings GK, Morse CI, Williams AG, Day SH.** Variability and distribution of muscle strength and its determinants in humans. *Muscle Nerve* 49: 879–886, 2014. doi:10.1002/mus.24075.
51. **Takken T, van Bergen MW, Sakkers RJ, Helders PJ, Engelbert RH.** Cardiopulmonary exercise capacity, muscle strength, and physical activity in children and adolescents with achondroplasia. *J Pediatr* 150: 26–30, 2007. doi:10.1016/j.jpeds.2006.10.058.
52. **Tolfrey K, Barker A, Thom JM, Morse CI, Narici MV, Batterham AM.** Scaling of maximal oxygen uptake by lower leg muscle volume in boys and men. *J Appl Physiol (1985)* 100: 1851–1856, 2006. doi:10.1152/japplphysiol.01213.2005.
53. **Tomlinson DJ, Erskine RM, Winwood K, Morse CI, Onambélé GL.** The impact of obesity on skeletal muscle architecture in untrained young vs. old women. *J Anat* 225: 675–684, 2014. doi:10.1111/joa.12248.
54. **Tonson A, Ratel S, Le Fur Y, Cozzone P, Bendahan D.** Effect of maturation on the relationship between muscle size and force production. *Med Sci Sports Exerc* 40: 918–925, 2008. doi:10.1249/MSS.0b013e3181641bed.
55. **Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J, Trappe T.** Single muscle fibre contractile properties in young and old men and women. *J Physiol* 552: 47–58, 2003. doi:10.1113/jphysiol.2003.044966.
56. **Trappe S, Williamson D, Godard M, Porter D, Rowden G, Costill D.** Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol (1985)* 89: 143–152, 2000. doi:10.1152/jappl.2000.89.1.143.
57. **Tsaopoulos DE, Baltzopoulos V, Maganaris CN.** Human patellar tendon moment arm length: measurement considerations and clinical implications for joint loading assessment. *Clin Biomech (Bristol, Avon)* 21: 657–667, 2006. doi:10.1016/j.clinbiomech.2006.02.009.
58. **Urbanchek MG, Picken EB, Kalliainen LK, Kuzon WM Jr.** Specific force deficit in skeletal muscles of old rats is partially explained by the existence of denervated muscle fibers. *J Gerontol A Biol Sci Med Sci* 56: B191–B197, 2001. doi:10.1093/gerona/56.5.B191.