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Age-related degenerative functional, radiographic, and histological changes of the shoulder in nonhuman primates

Johannes F. Plate, MD[a,b,*], Christopher M. Bates, BS[a,c], Sandeep Mannava, MD, PhD[a,b], Thomas L. Smith, PhD[a], Matthew J. Jorgensen, PhD[d], Thomas C. Register, PhD[d], John R. Stehle, PhD[e], Kevin P. High, MD[e], Carol A. Shively, PhD[d], Jay R. Kaplan, PhD[d], Katherine R. Saul, PhD[a,c], Christopher J. Tuohy, MD[a]

[a]*Department of Orthopaedic Surgery, Wake Forest School of Medicine, Winston-Salem, NC, USA*
[b]*The Neuroscience Program, Wake Forest University Graduate School of Arts and Sciences, Winston-Salem, NC, USA*
[c]*Department of Biomedical Engineering, Wake Forest School of Medicine, Winston-Salem, NC, USA*
[d]*Department of Pathology (Comparative Medicine) and the Wake Forest Primate Center, Wake Forest School of Medicine, Winston-Salem, NC, USA*
[e]*Department of Internal Medicine, Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA*

Background: Nonhuman primates have similar shoulder anatomy and physiology compared to humans, and may represent a previously underutilized model for shoulder research. This study sought to identify naturally occurring bony and muscular degeneration in the shoulder of nonhuman primates and to assess relationships between structural and functional aspects of the shoulder and measures of physical function of the animals. We hypothesized that age-related degenerative changes in the shoulders of nonhuman primates would resemble those observed in aging humans.
Methods: Middle-aged ($n = 5$; ages 9.4-11.8 years) and elderly ($n = 6$; ages 19.8-26.4 years) female vervet monkeys were studied for changes in mobility and shoulder function, and radiographic and histologic signs of age-related degeneration.
Results: Four out of 6 (4/6) elderly animals had degenerative changes of the glenoid compared to 0/5 of the middle-aged animals ($P = .005$). Elderly animals had glenoid retroversion, decreased joint space, walked slower, and spent less time climbing and hanging than middle-aged vervets ($P < .05$). Physical mobility and shoulder function correlated with glenoid version angle ($P < .05$). Supraspinatus muscles of elderly animals were less dense ($P = .001$), had decreased fiber cross-sectional area ($P < .001$), but similar amounts of nuclear material ($P = .085$). Degenerative rotator cuff tears were not observed in any of the eleven animals.

This study has been approved by the Institutional Animal Care and Use Committee (A-10-258). This project is taken in part from a dissertation submitted to the Neuroscience Program, Wake Forest University Graduate School of Arts and Sciences, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

*Reprint requests: Johannes F. Plate, MD, Department of Orthopaedic Surgery, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1070, USA.
E-mail address: jplate@wakehealth.edu (J.F. Plate).

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Discussion and conclusion: The vervet monkey naturally undergoes age-related functional, radiographic and histological changes of the shoulder, and may qualify as an animal model for selected translational research of shoulder osteoarthritis.
Level of evidence: Basic Science Study, in-vivo Animal Model.

Keywords: Animal model; vervet monkey; shoulder; rotator cuff; osteoarthritis; aging; degeneration

The study of age-related changes in the musculoskeletal system has become increasingly important in light of the growing proportion of the older population. Age-related pathology of the shoulder including osteoarthritis and rotator cuff tears may lead to marked disability and pain affecting activities of daily living. Approximately 13%-26% of individuals older than 70 years are affected by shoulder pain.[29] The prevalence of rotator cuff tears increases with age to approximately 40-50% in individuals over 50 years of age.[47,55] In 2006, approximately 30,000 total shoulder arthroplasties were performed, mainly for the treatment of symptomatic shoulder osteoarthritis.[1] With increased life expectancy and higher activity levels of the aging population, the prevalence of shoulder pathology including rotator cuff tears and degenerative shoulder disease is expected to increase,[34] warranting further research of the underlying pathophysiologic mechanisms of aging in the shoulder.

Various animal models have been established for the study of the natural history and underlying pathomechanism of shoulder pathology (Table I).[8,10,28,44] Ideally, these models would reproduce human age-related conditions including decreased muscle function and healing potential,[7] sarcopenia,[7,34,35] and other anatomical features. Sarcopenia is characterized by loss of muscle mass, generalized replacement of muscle fibers by fat, increased fibrosis, and decreased muscle force production.[7,35] Small animals (mouse, rat, and rabbit) have been widely used for shoulder research. The rat has similar anatomic features[8,10,44] and has become an indispensable model for studying shoulder degeneration,[31,45] including surgically-induced rotator cuff tears[10,31,44] tendon-to-bone healing,[3] muscular changes following injury,[2,45] and biologically enhanced repair strategies.[8] However, rat studies limit translation to human, because rats are quadrupedal with weight bearing forelimbs; they have limited overhead and multidirectional shoulder movement, and they are small.[9,15] Larger animal models, including the rabbit,[8,19,20,36,37] dog,[9] and sheep,[14,49] share pathophysiological features of shoulder degeneration; however, the acromion and the coracoid process are small or not present, which differs from human shoulder anatomy.[8]

In a comparative study of shoulder anatomy in various laboratory animals, the insertional structure of the rotator cuff tendons (supraspinatus, infraspinatus, and teres minor) on the greater tuberosity of the humeral head varied considerably among species.[43] Despite the similar anatomy between nonhuman primates and humans, only 1 study of rotator cuff pathology and healing following rotator cuff tear repair has been performed in a non human primate model.[42] Naturally occuring degeneration of the shoulder in nonhuman primates has not been assessed.

The present study offered a unique opportunity to characterize age-related degenerative changes of the shoulder in a species of nonhuman primates commonly used in biomedical research.[5] This study sought to identify naturally occurring bony and muscular degeneration of the shoulder in relation to the functionality of the animals to determine if age-related degeneration in vervets is consistent with aging human patients. A nonhuman primate model of age-related degenerative shoulder disease has the potential to overcome the various limitations of other animal models and allow the assessment of the natural aging process in an animal similar to human anatomy and upper extremity function.

Materials and methods

Adult female vervet monkeys (*Chlorocebus pygerythrus*) were selected to represent ‘‘middle-age’’ (n = 5; mean age 10.8 years; range, 9.4-11.8 years; approximate human age 30-45 years old) and ‘‘elderly’’ (n = 6; mean age 23.0 years; range, 19.8-26.4 years; approximate human age 70-95 years old) primates from a population of a vervet research colony established from animals captured on St. Kitts Island in the 1970s.[11,32] Early reports considered vervets 13 years of age as elderly[6]; however, the life expectancy of vervets in captivity has been revised such that animals above 20 years of age are now considered elderly. The 26-year-old animal in the current report represents the oldest female vervet monkey originating from this colony. All procedures were conducted in compliance with state and federal laws, standards of the U.S. Department of Health, and Human Services, and regulations and guidelines established by the Institutional Animal Care and Use Committee. The institution is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

All animals were housed among social groups of approximately 15-40 animals, allowed to roam freely in large, inside/outside pens (30 m^2), and to feed *ad libitum*. The assessment of animal mobility and physical function has been described previously.[41] Walking speed was recorded as the time necessary to walk a defined distance on various structures inside the pen. The time spent climbing and hanging was observed during 15-minute focal observation on separate days for each animal. Full-body computed tomography (CT) scans were performed on sedated animals (Ketamine) using a 32-slice CT scanner (Toshiba Aquilion; Toshiba America Medical Systems, Tustin, CA, USA) with 350 μ isotropic resolution and 0.5 mm slices just prior to the end of the study.

Table I Comparison of various animal models utilized for shoulder research

	Rat/Mouse	Rabbit	Dog	Sheep/Goat	Nonhuman primates
Advantages	- Comparable rotator cuff anatomy with supraspinatus tendon translating underneath an enclosed arch - Widely available and inexpensive - Lowest demand (care, facilities) - Large sample size	- Fibrofatty infiltration following injury - Relatively inexpensive - Low demand (care, facilities)	- Assessment of tendon-to-bone healing - Close to human size - Comparable biomechanical loads of the rotator cuff	- Use of standard human repair techniques - Assessment of tendon-to-bone healing - Close to human size	- Similar anatomy - Similar insertional rotator cuff tendon anatomy - Similar age-related degenerative changes of the shoulder - Use of standard human repair techniques - Multidirectional shoulder movement - Assessment of tendon-to-bone healing
Disadvantages	- Limited multidirectional movement of the shoulder - Small scale compared to human - Significant fatty infiltration following surgical rotator cuff injury only in combination with suprascapular nerve transection - Quadrupedal, weight-bearing - No re-tears following rotator cuff repair	- Limited comparability of anatomy - Use of subscapularis tendon - Quadrupedal, weight-bearing	- Limited multidirectional movement - Different anatomy of acromion and coracoid - Quadrupedal, weight-bearing - Moderate demand (care, facilities) - Expensive	- Limited multidirectional movement - Different anatomy - Use of infraspinatus tendon - Quadrupedal, weight-bearing - High demand (care, facilities) - Expensive	- Semi-terrestrial, weight-bearing forelimbs - Highest demand (care, facilities) - Highly expensive for longitudinal studies - Ethical concerns
Chronic rotator cuff tear condition	- Chronic rotator cuff tear partially persists, but spontaneous healing with scar-tissue forming a “pseudo-tendon”	- Chronic condition for muscular changes - Spontaneous healing	-Spontaneous healing with scar tissue	- Spontaneous healing with scar tissue	- Healing response to chronic injury has not been assessed
Outcome measures	- Functional in vivo assessment - Gait analysis - Histological analysis - CT, MRI	- CT, MRI, ultrasound - Gait analysis - Histological analysis	- CT, MRI, ultrasound - Gait analysis - Histological analysis	- CT, MRI, ultrasound - Histological analysis	- CT, MRI, ultrasound - Histological analysis - Assessment of physical activity, walking speed, and functional use of upper extremity and overhead activity

(*continued on next page*)

Table I (*continued*)

	Rat/Mouse	Rabbit	Dog	Sheep/Goat	Nonhuman primates
Areas of research	- Pathomechanism of age-related degeneration, intrinsic and extrinsic rotator cuff injury (impingement, overuse) - In vivo functional biomechanic studies - Molecular pathways - Rehabilitation	- Pathomechanism of muscular changes - Biomechanical studies - Tendon-to-bone healing with/without scaffold augmentation	- Tendon-to-bone healing with/without scaffold augmentation - Biomechanical studies - Mechanical strength of repair techniques	- In vivo biomechanical assessment of chronic rotator cuff tears - Mechanical strength of repair techniques	- Pathomechanism of age-related degeneration -In vivo tendon-to-bone healing - Biomechanical studies - Molecular pathways -Mechanical strength of repair techniques
Cost per animal (US Dollars)*	CD-1 mouse: $8, Lewis rat: $40	New Zealand White Rabbit: $100-$200	Hound: $1000	Sheep/Goat: $1000	$2500-$5000[24]
Approximate per diem rates per animal (US dollars)**	$1	$4	$14	$17	$10

CT, computer tomography; *MRI*, magnetic resonance image.
* Mean approximate cost for illustration. Prices may vary by vendor, institution, and type of animal (species, age, strain).
** Mean per diem rates according to the Animal Resource Program at 2 U.S. academic institutions as of 10/2012.

The investigators were blinded to the age of the animals during assessments of shoulder function, CT measurements, and histological sample analysis. Degenerative changes of the glenohumeral joint were evaluated on 2-dimensional (2D) coronal CT images and were graded according to the Kellgren and Lawrence (KL) classification system.[23] Three-dimensional (3D) CT-image reconstructions (AquariusNET; TeraRecon, Foster City, CA, USA) were used an adjunctive method to identify glenoid deformity and osteophytes. The joint space was measured on axial 2D CT scans as the shortest distance between the humeral head and the glenoid fossa.

The glenoid version angle was assessed from 3D reconstructed images that were re-sliced to create an axial section. The version angle was measured with a line drawn connecting the anterior and posterior glenoid rim relative to a line tangent to the body of the scapula; negative angles indicating retroversion and positive angles indicating anteversion. Retroversion of the glenoid on CT scans has been found to correspond to degenerative wear of the posterior articular surface or glenoid dysplasia.[53] The presence of partial and/or full thickness rotator cuff tears as discontinuity of the supraspinatus and/or infraspinatus tendon was assessed on coronal CT images. The acromio-humeral distance (AHD) was measured to assess superior translation of the humeral head using 2D CT image reconstructions which were standardized by setting the axes parallel to the short and long axes of the scapular body.[27]

The supraspinatus muscle, which is involved in degenerative pathology of the shoulder and is the most commonly torn rotator cuff tendon,[22] was assessed for structural changes on saggital 3D reconstructed CT images. Muscle density was measured in Hounsfield units from a 2×2 cm region of the supraspinatus muscle in the suprascapular fossa midway along the length of the scapular spine in a plane parallel to the scapular spine in line with the scapular body using the region of interest (ROI) tool embedded in the AquariusNET software.[51]

Animals were euthanized as part of another ancillary study designed to explore the effects of age on immune function and physiologic parameters of relevance to human health. The ancillary study protocol did not impact the findings of this study. Bilateral intact cadaveric shoulder specimens were obtained at necropsy for further analysis. The left supraspinatus muscles were excised, split into superficial and deep muscle portions, and then fixed in 10% neutral buffered formalin for 36 hours. These specimens were used for histological analysis of muscle fiber cross-sectional area and immunohistochemical analysis of nuclear material content. Specimens were embedded in paraffin, cut into 5-μm-thick cross-sections, placed on glass slides, and stained with hematoxylin and eosin (H&E) or 4,6-diamidino-2-phenylindole (DAPI). Images were obtained at 200x magnification (Zeiss M1 microscope with ImagePro® Plus v.6.3; Carl Zeiss, Jena, Germany). Three images per slide of 2 deep and 2 superficial samples were obtained and analyzed for a total of 12 images per specimen.[31]

Muscle fiber cross-sectional area (FCSA) was measured as the mean of 56.8 orthogonally-cut muscle fascicles per sample by outlining representative muscle fibers with the ROI tool imbedded in ImageJ software (National Institute of Health, Baltimore, MD, USA). A modified counting procedure was used to quantify the fluorescence of nuclei on DAPI stained images.[21] This method was evaluated for accuracy and precision by comparing it to the manual counting of 4 randomly chosen images, which yielded a maximum deviation of ±1.2%.

Table II Age, walking speed, and percent of time spent hanging and climbing between middle-aged and elderly animals

	Age (y)	Walking (cm/sec)	Climbing (% of time)	Hanging (% of time)
Middle-aged, n = 5	10.8 ± 0.44	59.42 ± 4.47	1.0 ± 0.1	0.5 ± 0.2
Elderly, n = 6	23.0 ± 1.05	48.80 ± 4.44	0.5 ± 0.2	0.2 ± 0.1
P value*	<.001	.129	.076	.187

* A *P* value of <.05 was considered statistically significant.

Statistical analysis of animal physical function, differences in joint space, version angle, muscle density, and histological measurements were assessed using independent Student *t* tests (SPSS Statistics 19; IBM Corp, Armonk, NY, USA). Linear regression analysis was performed to assess the correlation between glenoid version angle and functional measurements. Degenerative changes on CT images were compared using chi-square analysis. All statistical analyses were performed with alpha 0.05 and data are presented as mean ± the standard error of the mean (SEM). Figures were computed using Prism 5 (GraphPad Software Inc, La Jolla, CA, USA).

Results

Elderly animals exhibited significantly decreased physical mobility and function (Table II, Fig. 1). The glenoid of elderly animals was significantly retroverted (−2.2° ± 0.5°) compared to middle-aged vervets (2.6° ± 0.5°, $P < .001$, Fig. 2), and there was a significant correlation between age and glenoid version angle (Fig. 1). Walking speed ($P = .129$) and the time spent climbing ($P = .076$) and hanging ($P = .187$) tended to be reduced in elderly animals compared to middle-aged animals (Table II) and there was a significant correlation between glenoid version angle and functional parameters for the animals as a group (Fig. 1).

Shoulders in 4 of 6 animals in the elderly group (8 shoulders, 67%) had degenerative changes of the glenoid and humeral head with osteophyte formation on the posterior/inferior glenoid while no gross degenerative changes were observed in any of the middle-aged animals ($P = .005$) (Fig. 3). Two of the 8 shoulders were classified as KL Grade 1, 3 shoulders as Grade 2, 1 shoulder as Grade 3, and 2 shoulders in 1 elderly animal as Grade 4 changes with massive osteophyte formation, humeral head deformity, and joint space narrowing (Table III, Fig. 4). The mean joint space in elderly animals (0.55 ± 0.04 mm) was significantly decreased compared to the joint space in middle-aged animals (0.69 ± 0.02 mm, $P = .003$).

On macroscopic evaluation of the cadaveric shoulder specimens, no partial or full thickness rotator cuff tears were observed in any animal. Concurrently, there was no significant difference in AHD between middle-aged and elderly animals (5.5 ± 0.3 mm vs 6.8 ± 1.0 mm, $P = .27$), indicating a normally positioned humeral head. The AHD measurement in the animal with KL Grade 4 was difficult to determine and was increased compared to other animals due to high grade deformity and osteophyte formation (Fig. 3, *B*). The supraspinatus muscles of elderly animals were significantly less dense according to Hounsfield unit measurements on CT-images compared to middle-aged animals (87.0 ± 0.8 vs 91.5 ± 0.8, $P = .004$) (Fig. 5).

Histological analysis of the supraspinatus muscle in elderly animals revealed significantly decreased FCSA in the superficial portion compared to middle-aged animals (Fig. 6, $P < .001$) and similar FCSA in the deep portion (Fig. 6, *B*, $P = .696$). Overall, middle-aged muscle (Fig. 7, *A*) appeared more compact and organized on H&E stains compared to elderly animals (Fig. 7, *B*), whose muscle fibers were disorganized with atrophic changes. Quantification of DAPI fluorescence revealed significantly greater amounts of nuclear material in elderly animals in the superficial portion of the supraspinatus muscle compared to middle-aged animals (284.4 ± 13.4 μm^2 vs 223.2 ± 9.6 μm^2, $P = .001$). However, there was no difference in DAPI fluorescence in the deep portion of the supraspinatus between middle-aged and elderly animals (280.9 ± 12.2 μm^2 vs 313.6 ± 15.7 μm^2, $P = .115$). There was no gross fatty infiltration noted in any of the middle-aged or elderly muscle sections.

Discussion

This study sought to identify and characterize naturally-occurring age-related degenerative changes of the shoulder joint in known-aged adult and elderly female vervet monkeys. Sixty-seven percent of the elderly animals in this study had significant degenerative changes in their shoulders compared to middle-aged animals based on the evaluation of CT images for signs of osteoarthritis. The glenoid retroversion and significantly smaller joint space in elderly animals were similar to age-related degenerative changes observed in osteoarthritis with cartilage wear in human subjects.[53] Walch et al assessed 113 osteoarthritic shoulders using CT image measurement techniques similar to the current study and found increased glenoid retroversion in 41% of cases.[53] Glenoid version angle significantly correlated with age, with an increase in glenoid retroversion with increased age. Physical mobility and shoulder function were significantly correlated with glenoid version angle, highlighting glenoid retroversion as a potential determinant of physical function. Animals with glenoid retroversion as a marker of osteoarthritic degeneration were less mobile and physically active regardless of age. The anatomical

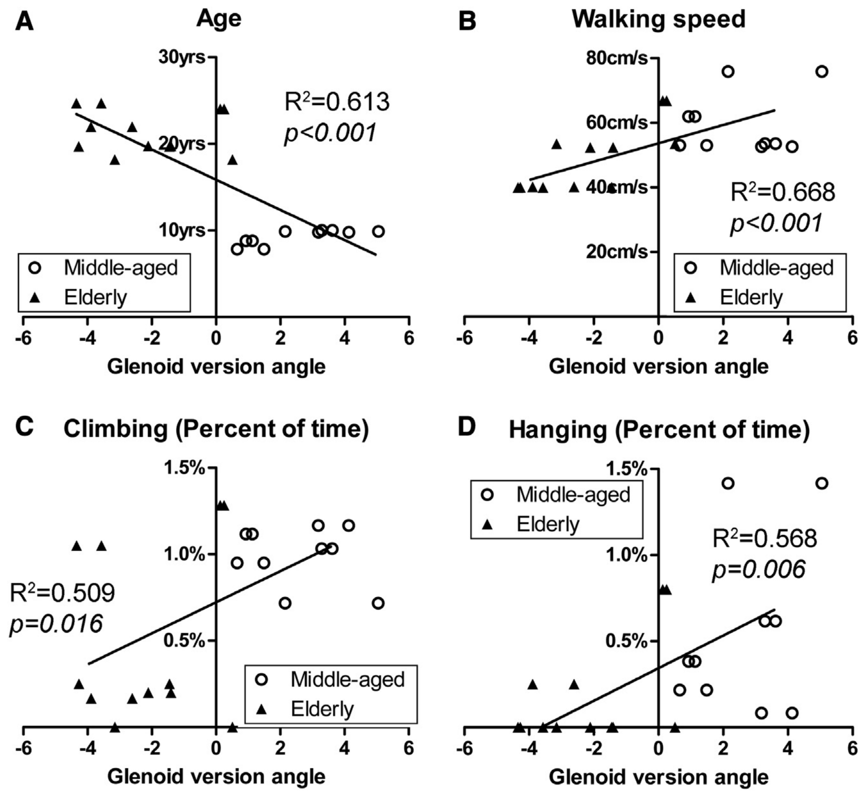

Figure 1 Age (**A**), walking speed (**B**), the percent of time spent climbing (**C**), and hanging (**D**) significantly correlated with glenoid version angle. Considering all animals as a single group, all functional parameters decreased with negative version angles (retroversion) and increased with positive version angles (anteversion). R^2 is reported for each functional parameter. Correlation was considered significant for $P < .05$.

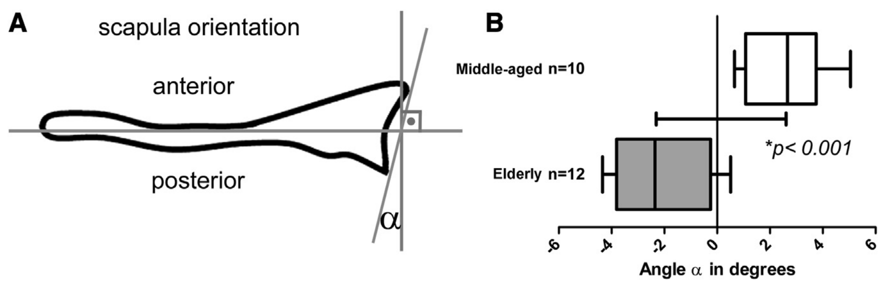

Figure 2 Radiographically determined glenoid version angle is reduced in elderly animals. (**A**) The glenoid version angle (α) was obtained from axial CT-scans of the shoulder and measured in relation to a line along the scapula and the anterior and posterior rim of the glenoid. (**B**) Box plot of the glenoid version angle by age group. Elderly animals had a significantly lower mean version angle (greater retroversion) of the glenoid compared to middle-aged animals ($P < .001$).

changes of the glenoid during aging, taken together with the significant relationship of glenoid version with physical mobility, establishes the vervet monkey as an animal model for glenoid degenerative disease and age-related disuse of the upper limb. This work provides a foundation for future studies of shoulder degenerative disease. Our results also support glenoid alignment as an important marker for upper limb mobility and function, which illuminates this as an area for future research in this animal model and in the clinical population.

The histologic changes in the supraspinatus muscles found in elderly animals in this study were similar to degenerative changes observed in humans during aging. The decrease in FCSA in the superficial portion of the supraspinatus muscle in elderly vervets is consistent with decreased contractile elements and muscle fiber atrophy in humans.[52] Aging skeletal muscle is subject to increasing oxidative stress, neuromuscular junction degeneration, declining trophic support, and transformation of muscle fiber-type leading to atrophic changes.[4,38] Quantified total nuclear material was similar between the 2 groups according to DAPI stains, but showed a trend toward increasing in the elderly group. Correlated with significant superficial FCSA reduction, the elderly group muscle fiber

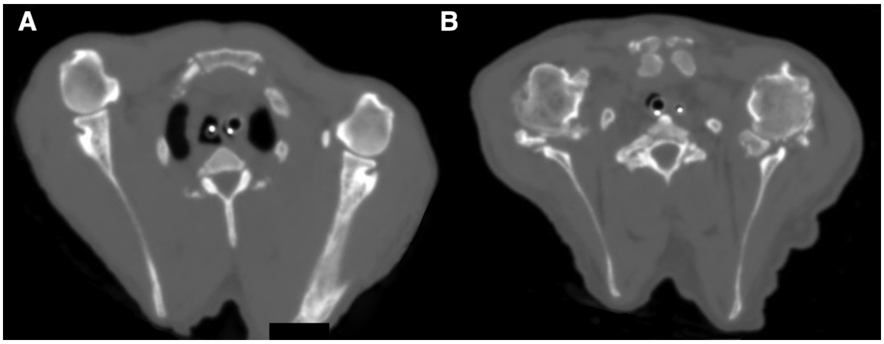

Figure 3 Representative axial CT images of a middle-aged (**A**) and an elderly (**B**) vervet monkey shoulder. The elderly animal exhibited marked glenoid degeneration with osteophyte formation.

Table III Kellgren and Lawrence classification of radiographic appearance of osteoarthritis

Osteophyte formation	Joint space narrowing	Subchondral sclerosis	Deformity	Grade	Middle-aged vervet shoulders, n = 10	Elderly vervet shoulders, n = 12
None	None	None	None	0	10	4
Possible	Possible	None	None	1		2
Definitive	Mild	Possible	None	2		3
Moderate size, multiple	Moderate	Mild	Possible	3		1
Large size	Marked	Severe	Definitive	4		2

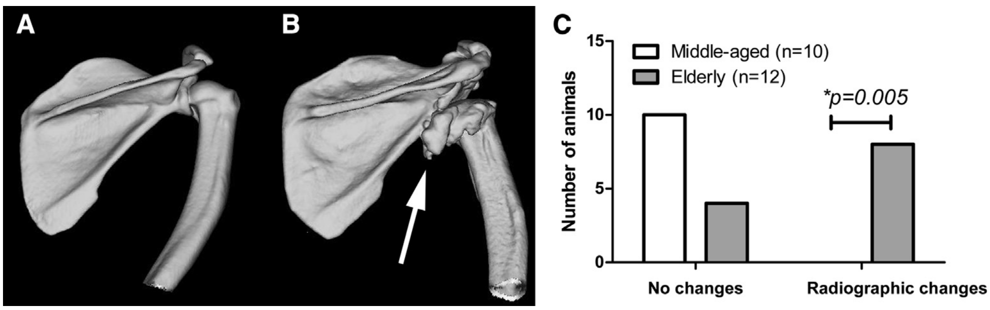

Figure 4 Radiographic demonstration of age related pathologies in the shoulder of the vervet monkey. Representative 3D reconstructed CT images of the right shoulder from a middle-aged (**A**) and elderly (**B**) animal. Noteworthy are the marked cartilage loss and osteophytic changes in the elderly animal (*white arrow*). (**C**) Frequency histogram of shoulder degeneration detectable by CT scan in middle-aged versus elderly animals demonstrating significant age related degenerative changes ($P = .005$).

nuclei may have a reduced myonuclear domain consistent with age-related atrophy.[4,12] The myonuclear domain describes the relation between muscle FCSA and the number of myonuclei that support the muscle fiber.[12,40] However, the deep portion of the supraspinatus in elderly animals revealed similar FCSA compared to middle-aged animals, which may indicate that the supraspinatus muscle layers degenerate at different rates. In human type II thigh muscles, the FCSA correlates with age[52]; therefore, an asymmetric distribution of type I versus type II muscle fibers may explain this depth-dependent atrophic variation.

Degenerative rotator cuff tears are common in the aging human population with a prevalence of nearly 50% in adults over the age of 70 years.[56] Despite the age-related changes observed in this study, no grossly visible rotator cuff tears were observed in this subset of 6 elderly vervets on macroscopic inspection. AHD was similar in both groups, showing that age-related degeneration did not lead to superior translation of the humeral head in these animals. The measurement of supraspinatus atrophy and fatty infiltration following rotator cuff tear was first described by Goutallier et al using CT scans[17] to identify patients with poor predicted outcomes.[18,33] Fatty infiltration of skeletal muscle is characterized by a decrease in Hounsfield units obtained from CT images as a measure of X-ray attenuation.[16,39] With magnetic resonance imaging (MRI) becoming the standard diagnostic tool for rotator cuff tears, the Goutallier

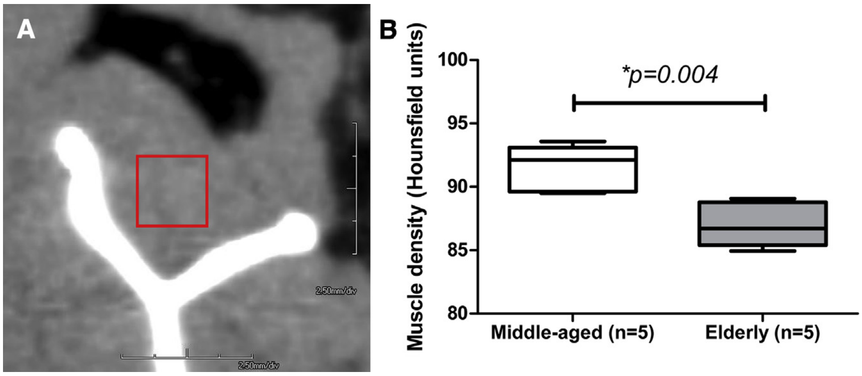

Figure 5 **A**, Supraspinatus density was measured in Hounsfield units on sagittal 3D CT-reconstructions using an image slab. A 2 × 2 cm region of the muscle midsubstance was evaluated using the region of interest tool inherent to the software (AquariusNET). **B**, Middle-aged animals had significantly greater muscle density compared to elderly animals ($P = .004$).

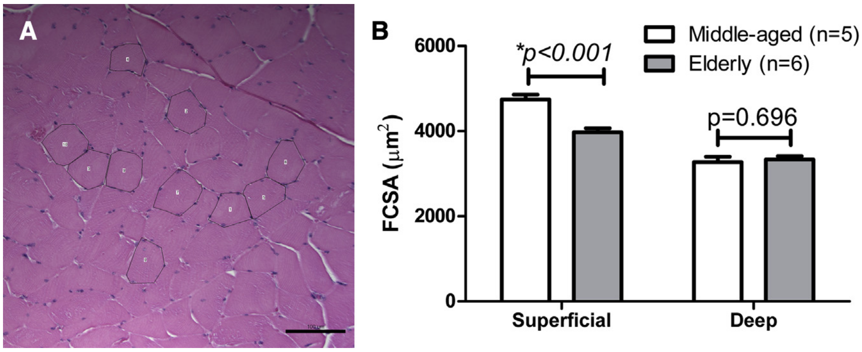

Figure 6 Muscle fiber cross-sectional area (FCSA) was measured on Hematoxylin and Eosin stained 5-μm thick tissue samples (**A**) with the ImageJ software. In the superficial portion of the supraspinatus muscle, middle-aged animals revealed a greater FCSA compared to elderly animals (4740 ± 118.8 μm^2 vs 3971 ± 98.0 μm^2, $P < .001$) (**B**). There was no difference in FCSA in the deep portion of the muscle between middle-aged and elderly animals (3274 ± 123.2 μm^2 vs 3331 ± 84.2 μm^2, $P = .696$).

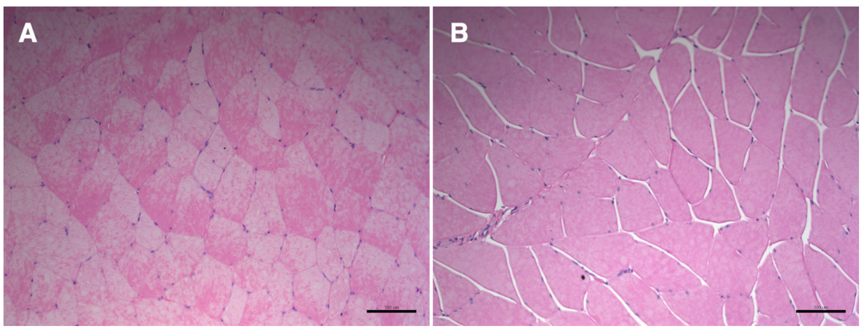

Figure 7 Representative Hematoxylin and Eosin stained slides at 200× magnification of the superficial layer of the supraspinatus muscle in middle-aged (**A**) and elderly (**B**) animals. The supraspinatus in middle-aged animals appeared to be more densely packed compared to elderly animals which revealed lower FCSA in the superficial portion of the muscle. The *scale bar* in the lower right corner represents 100 μm.

classification system has been expanded to MRIs.[13,54] However, MRIs only allow for qualitative assessment of fatty infiltration compared to quantative assessment with CT images used in the current study.[51] To our knowledge, there have been no previous reports on observed rotator cuff tears in free-roaming nonhuman primates. While the muscular changes observed in this study are similar to human changes of the rotator cuff, the absence of rotator cuff tears in elderly animals may exclude the vervet monkey as a model for prevalent naturally occurring degenerative rotator cuff tears. Future studies assessing the rotator cuff in the aging vervet monkey in vivo will preferably employ MRI imaging and include a larger cohort of animals.

The correlation of glenoid version angle with the time spent climbing and hanging suggests that degenerative changes of the shoulder may lead to physical disability.

Climbing and hanging from the upper extremity may approximate reaching overhead in the human population, an activity of daily living. Walking speed, which also correlated with glenoid version angle, may have been influenced by other co-morbid degenerative changes (eg, osteoarthritic changes of the knee, degenerative spine kyphosis) and cannot be solely attributed to shoulder dysfunction. The vervet monkey is semi-terrestrial animal, spending time on the ground as well as in trees, and is quadrupedal using the upper extremity for locomotion with limited weight-bearing. Therefore, the joint loading forces acting on the glenoid through the humeral head may be different compared to humans, which may explain the significant increase in glenoid retroversion with aging. While rotator cuff tendons in humans interdigitate and form a uniform insertion on the greater tuberosity, they insert separately in rodents, dogs, and sheep.[8,43] A uniform insertion of the rotator cuff tendons is found only in advanced nonhuman primates and the Australian tree kangaroo.[43] Furthermore, the supraspinatus muscle in vervet monkeys was found to act as dynamic stabilizer for the glenohumeral joint and initiator of arm elevation similar to humans.[25,26] In contrast, the commonly used rat model for shoulder research is quadrupedal with weight-bearing forelimbs and limited overhead and multidirectional movement of the shoulder.[9,15,46,48,50]

Only 11 female vervets were used in the current study, and sampling of a larger set of animals may have revealed evidence of rotator cuff tears. All animals were part of an ancillary study protocol assessing age, body composition, functional status, and immune function in female monkeys. Therefore, male specimens were unavailable for the current study, which warrants further analysis of the differences between age-related changes in male and female vervets in future studies. Another limitation of the study was the time between sacrifice of the animal and tissue fixation, which was variable and ranged from 30 to 100 minutes. One elderly animal died unexpectedly and the exact time from death to tissue fixation was unknown. These inconsistencies may have resulted in nonuniform staining of the sample but did not affect assessment of FCSA and nuclear content. All CT measurements were dependent on the resolution of the CT scanner (350 μ). Considering the size of the animals, it is possible that changes in joint space and glenoid version angle may have been over- or underestimated despite the high resolution of the CT images. In addition, the position of the humeral head on CT images was variable, as some elderly animals had kyphotic spine changes and could not be positioned in the customary supine position with arms crossed over the upper abdomen. In these cases, normal humeral head position had to be estimated and may have led to variability in joint space measurements.

The size of nonhuman primates, their similar anatomical features and comparable multidirectional motion of the upper extremities may overcome the limitations associated with other animal models (Table I). Only 5 studies using nonhuman primates for shoulder research were found between 2002 and 2012 in a search of the PubMed database of the U.S. National Library of Medicine,[30] suggesting that nonhuman primates may have been underutilized for shoulder research in the past. In comparison, 107 studies used small animal models, 84 studies used large animals (dog, sheep, goat), and 193 studies utilized human cadaveric specimens.[30]

Conclusion

Based on the findings of the current study and considering the inherent limitations of animal models, nonhuman primates experience age-related degenerative decline in physical function, and changes in muscular and bony shoulder structure. The shoulder of vervet monkeys may serve as a model of shoulder osteoarthritis with increasing glenoid retroversion with aging. However, degenerative rotator cuff tears were not present in aging vervet monkeys. While ethical concerns and financial constraints (cost per young animal $3,500 to $5,000; housing $2,000 to $5,500 US dollars per animal per year)[24] regarding the use of nonhuman primates must be recognized,[8,28] there is a potential benefit for their use in selected translational studies of shoulder degeneration.

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