The histopathology of the humeral head in glenohumeral osteoarthritis

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ABSTRACT

Objective: The histopathologic wear patterns in glenohumeral osteoarthritis (GOA) have not been described. The aims of the study were to a) describe the histopathology of humeral head wear patterns in patients with end-stage GOA and b) identify clinical and radiographic parameters that correlate with observed histopathological wear patterns.

Methods: Eighteen humeral heads from patients undergoing anatomic total shoulder arthroplasty for end-stage osteoarthritis were divided radially into eight wedge-shaped zones. Each zone was subdivided into central and peripheral regions. Histologic analysis included measurements of cartilage and subchondral bone plate thickness, subchondral bone area, and cartilage structure was scored using the Osteoarthritis Research Society (OARSI) and modified Mankin systems. Clinical variables including patient history, physical exam, functional evaluation, and radiographic assessments were evaluated for correlations with humeral head characteristics.

Results: Overall, humeral heads demonstrated a pattern of central and inferior cartilage damage, loss, and subchondral bone changes. However, within the group, composite maps of individual patient wear patterns demonstrated a sub-group of patients with a more focal inferior cartilage lesion. Greater pre-operative range of motion (in both upper extremities), higher pre-operative SANE and ASES scores, female sex, non-dominant extremity, concentric wear patterns, and smaller inferior osteophytes were associated with these focal lesions.

Conclusion: Humeral head cartilage wear patterns in GOA include central and inferior cartilage damage and loss. A histopathological distinction was identified between patients with more focal versus diffuse wear, which may manifest clinically with preservation of function and range of motion, and with less profound radiographical changes.

1. Introduction

Glenohumeral osteoarthritis (GOA) is common and leads to significant discomfort and disability. Conservative management sometimes progresses to operative treatments including arthroscopy and arthroplasty [1]. Though the overall severity of GOA may predict response to various treatments [2–4], the histopathologic basis of this severity is poorly defined. Further, while preoperative glenoid wear patterns are predictive of select outcomes following total shoulder arthroplasty [5–9], the implications of humeral head wear patterns are not well-understood. Previous descriptions of the degenerative patterns of the humeral head in GOA used quantitative imaging protocols [10–12], and histologic...
The macroscopic appearance of humeral head erosion most commonly associated with GOA has been described as a “Friar Tuck” pattern, with central eburnation and a surrounding ring of cartilage and osteophytes [14,15] (Supplemental Fig. 1A), but this appearance has not been confirmed histologically, nor have other phenotypes of humeral head wear been characterized. Altered joint mechanics can lead to progression of GOA [16–21], and we recently showed profound contracture, thickening, and inflammation of the glenohumeral joint capsule in GOA [22]. Following arthroscopic release of contracted capsular tissue, there is predictable improvement in glenohumeral range of motion [23,24], and size and location of cartilaginous lesions can be predictive of response to arthroscopic management of GOA [2,3], but the improvements in pain are more modest [25]. Thus, evaluating humeral head cartilage wear patterns together with clinical data, including pre-operative range of motion, is the critical next step in improved understanding of the connection between joint stiffness, capsular contracture, progression of GOA, and pain, and could eventually be useful in guiding patient management earlier in the disease process.

The aims of this study were to describe the histopathology of humeral head articular cartilage wear patterns in patients with end-stage GOA, and to identify if pre-operative clinical or radiographic parameters were associated with these patterns. We hypothesized that humeral head articular cartilage wear would follow a predictable pattern of central wear, and that patients with greater preoperative stiffness and more restricted range of motion would have a relatively more focal, and less diffuse pattern of cartilage damage.

2. Methods

2.1. Subjects

The study was approved by the Duke University IRB. A consecutive series of patients (n = 18) scheduled for elective anatomic total shoulder arthroplasty to manage GOA by a single surgeon (GEG) from 5/2017-11/2017 were recruited for this study at their preoperative clinic visit. Exclusion criteria for the study group included inflammatory arthritis, neurologic abnormalities affecting the ipsilateral shoulder, or known ipsilateral rotator cuff tear. Eleven patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) within six months of the date of surgery.

2.2. Clinical data

Through clinical chart review we gathered preoperative data including patient demographics, medical history, physical exam, pain, and patient-reported functional assessments (Table 1). Physical examination assessments, including range of motion (forward flexion, external rotation, internal rotation) (Supplemental Methods), were performed by the primary surgeon (GEG) at the time of the preoperative visit in all cases. Functional assessments included the Single Assessment Numeric Evaluation (SANE) and the American Shoulder and Elbow Surgeons (ASES) score [26,27] (Supplemental Methods).

Radiographic measurements including joint space integrity, Samilson and Prieto Classification [28], centricity of glenoid erosion, and Walch Classification [9,29] were recorded by the primary surgeon (GEG) in the clinical note at the time of the preoperative visit, and confirmed at the time of data collection (Supplemental Methods). Goutallier grades were assigned to the rotator cuff musculature based on appearance on CT, or MRI if available (Supplemental Methods) [30,31]. A summary of objective clinical measurements, including physical examination and radiographic assessments, appears in Table 2.
Fig. 1. (A) Resected humeral head demonstrating characteristic ‘Friar Tuck’ pattern resembling male pattern baldness. (B) Schematic of orientation of left and right humeral heads demonstrating position of superior and anterior notches made at surgery to preserve orientation, zones 1–8 and corresponding anatomic orientation, and inner (grey circle) central and outer peripheral regions graded histologically. Red rectangle represents surface of Zone 1 block cut and examined histologically.

Table 2
Preoperative objective patient variables.

| Category                        | Sub-category        | Percentage (%) | Mean   | Std Dev | Median | Minimum | Maximum |
|---------------------------------|---------------------|----------------|--------|---------|--------|---------|---------|
| External Rotation               | Affected            | 27             | 21     | 35      | 0      | 0       | 60      |
|                                 | Unaffected          | 50             | 18     | 48      | 10     | 10      | 80      |
| Forward Flexion                 | Affected            | 113            | 39     | 115     | 40     | 40      | 170     |
|                                 | Unaffected          | 158            | 17     | 160     | 120    | 120     | 180     |
| Internal Rotation               | Affected            | 18             | 4      | 20      | 10     | 10      | 22      |
|                                 | Unaffected          | 12             | 5      | 10      | 7      | 7       | 22      |
| Samilson and Prieto classification | 1 (mild)             | 1              | 6      |         |        |         |         |
|                                 | 2 (moderate)        | 4              | 22     |         |        |         |         |
|                                 | 3 (severe)          | 13             | 72     |         |        |         |         |
| Inferior osteophyte length (mm) | A1                  | 12.0           | 5.7    | 13.1    | 0      | 24.27   |         |
|                                 | A2                  |                |        |         |        |         |         |
|                                 | B1                  |                |        |         |        |         |         |
|                                 | B2                  |                |        |         |        |         |         |
| Walch                           | Normal              |                |        |         |        |         |         |
|                                 | Partial Loss        | 4              | 23     |         |        |         |         |
|                                 | Complete loss       | 14             | 77     |         |        |         |         |
| Joint Space                     | Normal              |                |        |         |        |         |         |
|                                 | Partial Loss        |                |        |         |        |         |         |
|                                 | Complete loss       |                |        |         |        |         |         |
| Wear Type                       | Concentric          |                |        |         |        |         |         |
|                                 | Eccentric           |                |        |         |        |         |         |

Histological grading was evaluated using the following: Cronbach’s alpha was calculated to assess reliability, Bland and Altman plots (Supplemental Fig. 1B-C) and inter- and intra-observer agreement were used to assess reproducibility, and inter-observer variability was assessed with the intraclass correlation and by calculating the proportion of scores within a 2-point match for OARSI and 3-point match for modified Mankin scoring systems. Intra-observer variability was assessed by the proportion of scores within 1-point match for OARSI and a 2-point match for the modified Mankin systems [36,37].

Histological scores and morphometry were compared by region and zone using the nonparametric all pairs Steel-Dwass method, with p < 0.05 reported as statistically significant. For evaluation of correlations between clinical data, and between clinical, histological and morphometric data, categorical variables were assessed with Fishers exact test, ordinal variables with Komogorov-Smirnov Asymptomatic test or Steel-Dwass all pairs method, and continuous variables were compared with Spearman’s rho, or Chi Square, as appropriate for various combinations of data type. Associations were reported at p < 0.05. JMP Pro 14.0.0 (SAS, Cary, NC, USA) was used for all statistical analyses.

3. Results

Pre-operative historical and demographic data are summarized in Table 1, and pre-operative clinical measures in Table 2. Histological measures of reliability and intra- and inter-observer reproducibility and variability are reported in Supplemental Table 1; Cronbach’s alpha was determined for the mean of the scores from all four observers across all sections, and was found to be > 0.9, or ‘excellent’ for both OARSI and modified Mankin systems. Bland and Altman plots (Supplemental Fig. 1B-C) with the upper and lower limits of agreement demonstrated lack of dependency, and modified Mankin and OARSI scoring systems were significantly and highly correlated for both central and peripheral regions (Supplemental Fig. 1D-E).

3.1. Cartilage and subchondral bone histomorphometry

Mean cartilage thickness was significantly (p < 0.0001) thinner centrally than in the periphery of the humeral head (Fig. 2A,B,C). Inferior regions (Supplemental Fig. 1D-E).

min), rinsed in tap water (10 min), then stained with a 0.05% solution of Fast Green (5 min). Slides were rinsed in 1% acetic acid and then stained in a 0.1% solution of Safranin O (5 min). Slides were dehydrated, cleared, and cover-slipped with resins media.

Four trained graders blinded to patient and section location evaluated each histological slide at three points in each of two regions (central and peripheral) using the modified Mankin grading system [32-34] as well as the Osteoarthritis Research Society (OARSI) grading system [35]. Cartilage damage was therefore mapped by 8 zones circumferentially around the humeral head across both peripheral and central regions, utilizing techniques published previously [33] (Fig. 1B). A subset of 10% of images were replicated during grading sessions to allow for calculation of inter- and intra-observer parameters.

Histomorphometry was performed at 6–8 sites for each Safranin O/ fast green section, yielding a minimum of n = 3 measurements for central and peripheral regions of each zone for each humeral head. Cartilage thickness was measured (CellSens; Olympus) from the cartilage surface to the tidemark, with cartilage loss to the tidemark, or eburnation of subchondral bone and loss of tidemark denoted as ‘0’ thickness, even if some calcified cartilage remained. Subchondral bone plate thickness was measured through the subchondral bone to the tidemark, with the recognition that subchondral bone plate thickness was underestimated in regions where there was eburnation or complete loss of tidemark. Additionally, subchondral bone area was measured (CellSens, Olympus) along the tide mark where possible to include the entirety of the subchondral bone plate along the 50% innermost (central) and 50% outermost (peripheral) regions of each section. At the intersection of subchondral bone plates with trabeculae, the measurements extended in orthogonally across the trabeculae at the level of the subchondral bone plate, thereby excluding the trabeculae.

2.5. Statistical analyses

Histological grading was evaluated using the following: Cronbach’s alpha was calculated to assess reliability, Bland and Altman plots (Supplemental Fig. 1B-C) and inter- and intra-observer agreement were used to assess reproducibility, and inter-observer variability was assessed with the intraclass correlation and by calculating the proportion of scores within a 2-point match for OARSI and 3-point match for modified Mankin scoring systems. Intra-observer variability was assessed by the proportion of scores within 1-point match for OARSI and a 2-point match for the modified Mankin systems [36,37].

Histological scores and morphometry were compared by region and zone using the nonparametric all pairs Steel-Dwass method, with p < 0.05 reported as statistically significant. For evaluation of correlations between clinical data, and between clinical, histological and morphometric data, categorical variables were assessed with Fishers exact test, ordinal variables with Komogorov-Smirnov Asymptomatic test or Steel-Dwass all pairs method, and continuous variables were compared with Spearman’s rho, or Chi Square, as appropriate for various combinations of data type. Associations were reported at p < 0.05. JMP Pro 14.0.0 (SAS, Cary, NC, USA) was used for all statistical analyses.
cartilage (zone 5) was thinner than superior-anterior (zone 2) centrally and peripherally, and at the periphery, inferior (zone 5) cartilage was also thinner than posterior (zone 7–8) and superior (zone 1–2). Subchondral bone area (Fig. 2D and E,F) was increased (sclerotic) centrally compared to peripherally (p < 0.0001). Subchondral bone area was similarly thick across all zones centrally, whereas in the periphery, the posterior (zone 7) was thinner than superior-anterior (zone 2), anterior (zone 3–4), and inferior (zone 5). Similarly, subchondral bone plate thickness (Fig. 2G and H,I) was significantly greater (sclerotic) centrally than in the periphery (p < 0.0001), but there were no differences circumferentially.

3.2. Histological scores of cartilage degradation

For both modified Mankin and OARSI histological scoring (Fig. 3), central regions (Fig. 3A,D) demonstrated significantly worse cartilage damage than peripheral regions (Fig. 3B,E) (p < 0.0001). There was no significant effect of zone for either modified Mankin or OARSI scores for zones located centrally. However, in the periphery, similar patterns were seen for modified Mankin and OARSI scoring systems; anterior (zone 4) and inferior (zone 5) were significantly worse than superior (zone 1) for modified Mankin (Fig. 3B). For OARSI, inferior (zone 5) was significantly worse than posterior (zone 7–8) (Fig. 3E).

3.3. Composite joint maps

When evaluating composite joint maps of individual patients (Fig. 4), together with observing high variability in scores for individual zones in the histomorphometric parameters identified, it was evident that some individuals (for example Patient 1 and Patient 15) had their primary area of cartilage damage restricted to the inferior aspect of the humeral head, while other individuals (for example Patient 10 and Patient 14) had a more typical ‘Friar Tuck’ pattern of both inferior and central cartilage loss and subchondral bone eburnation. These differences were also evident on heat maps examining the histomorphometric parameters when the overall group (n = 18) was divided into patients with complete cartilage thickness loss in no more than one zone in the central region (n = 6), compared to patients with more extensive cartilage loss across several zones or regions (n = 12) (Supplemental Fig. 1F).

3.4. Correlations between clinical, demographic, and imaging parameters

Increasing age was correlated with lower pre-operative pain scores and higher SANE scores (Fig. 5). In addition, female sex was correlated with concentric rather than eccentric glenoid wear patterns. A low number of comorbidities was associated with a Samilson and Prieto grade of 3, indicating a larger inferior osteophyte, compared to lower grades. Pre-operative body mass index was only associated with increasing internal rotation in the contralateral shoulder. High pre-operative SANE scores were also associated with less severe joint space loss. Range of motion parameters were tightly correlated with each other [data not shown], both in the affected upper extremity and in the contralateral upper extremity, and range of motion in forward flexion and external rotation was positively correlated with ASES score (Fig. 5).

3.5. Correlations of clinical, demographic and imaging parameters to microscopic analyses

All associations of pre-operative clinical, demographic and imaging parameters with regional and zonal cartilage thickness (Fig. 6A), subchondral bone area (Fig. 6B) and subchondral bone plate thickness (Fig. 6C), and to modified Mankin (Fig. 7A) and OARSI (Fig. 7B) scores were examined. Only those correlations that applied across multiple zones or regions for the outcome measures are discussed here; a full list of
Significant correlations are reported in Supplemental Table 2.

Concentric glenoid wear pattern was associated with increased central cartilage thickness in superior-posterior (zones 7, 8, I) (Fig. 6A). In contrast, eccentric wear was associated with overall worse modified Mankin scores (Fig. 7A), specifically in posterior central, (zone 7) and posterior superior (zone 8).

Fig. 3. Modified Mankin (A, B, C) and OARSI (D, E, F) histology scores for central (A, D) and peripheral (B, E) regions circumferentially for zone 1–8 of resected humeral heads. Heat maps summarizing findings for Modified Mankin scores (C) and OARSI scores (F). Nonparametric comparisons for all pairs using the Steel-Dwass method. Black line p < 0.05 between zones. Grey box: central region significantly different from periphery, for both modified Mankin and OARSI scoring system.

Fig. 4. Stitched Safranin O/Fast Green histology images in the Superior-Inferior and Anterior-Posterior planes for four representative patients demonstrating considerable variability in the extent of cartilage loss and eburnation of subchondral bone (Patients 10, 14), compared to relatively focal inferior loss of cartilage (Patients 1, 15) in others.

Fig. 5. Summary of significant associations between demographic, clinical and imaging variables recorded. Complete list of associations, statistical tests, and test results are reported in Supplemental Table 2. Green arrows between two variables indicate a significant (p < 0.05) positive association, whereas red dashed-dotted arrows between two variables indicate a significant (p < 0.05) negative association.
worse modified Mankin and OARSI scores (Fig. 7) in the superior-anterior (zone 2) centrally. Inferior osteophytes were larger in patients with less preservation of cartilage thickness at the periphery of the anterior of the humeral head (Fig. 6A), and with increased subchondral bone area though the majority of the periphery (zone 2–4, 6–8) (Fig. 6B), but was not associated with subchondral bone plate thickness (Fig. 6C) or histological scores (Fig. 7).

High pre-operative pain scores were associated with thicker peripheral cartilage (Fig. 6A) and thicker subchondral bone (Fig. 6C) in anterior-inferior (zone 4), but was not associated with cartilage damage scores (Fig. 7). High SANE scores; however, were associated with increased subchondral bone area in peripheral anterior zone 3 (Fig. 6B), and with less total cartilage damage (lower modified Mankin score) in central posterior (zone 7) (Fig. 7A), and superior-anterior (zone 2) (OARSI) (Fig. 7B). High ASES scores were associated with a thicker subchondral bone plate in central superior-anterior (zone 2) and in multiple zones around the periphery (zones 1,3,4,6,7) (Fig. 6B). High ASES scores were also associated with low (less damage) peripheral modified Mankin scores (Fig. 7A), particularly in posterior-inferior zone 6, and with low (less damage) peripheral OARSI scores, particularly in superior-anterior (zone 2), and inferior (zone 5) (Fig. 7B).

Largely in disagreement with our initial hypothesis however, in
general retention of pre-operative range of motion was associated with more focal cartilage lesions. Unexpectedly, some of these associations in the central region of the humeral head related more to pre-operative range of motion in the contralateral, instead of the operated upper extremity. Preservation of cartilage thickness (Fig. 6A) and increased subchondral bone plate thickness (Fig. 6C) in the central region of posterior and posterior-inferior (zone 6 & 7) humeral head was associated with higher range of motion in forward flexion and external rotation in the contralateral upper extremity, whereas increased subchondral bone area (Fig. 6B) in the posterior (zone 7) humeral head was associated with decreased internal rotation in the contralateral upper extremity. In the peripheral region, pre-operative range of motion in the operative shoulder was more frequently associated with cartilage (Fig. 6A) and subchondral bone plate thickness (Fig. 6C) parameters, with preservation of cartilage thickness in superior-anterior (zone 2) associated with high pre-operative external rotation, but low internal rotation in superior (zone 1) (Fig. 6A). High pre-operative external rotation in the operative extremity was associated with increased subchondral bone plate thickness in the periphery of superior (zone 1) and posterior (zone 7) regions (Fig. 6C). Modified Mankin and OARSI scores were associated with many range of motion parameters, with lower range of motion in both operative and contralateral extremity associated with higher (worse damage) histological scores (Fig. 7). Notably; however, internal rotation was not associated with cartilage damage, and low external rotation in the operative extremity was associated with more cartilage damage in the greatest number of regions and zones (Fig. 7).

Finally, while no shoulders had a full thickness rotator cuff tear, some did have fatty infiltration of the rotator cuff muscles on CT or MRI. However, only Goutallier grade of the supraspinatus was associated with more than one histomorphometric outcome measure; increased Goutallier grade for the supraspinatus was associated with increased subchondral bone area in the periphery of inferior (zone 5) and with lower OARSI score (less cartilage damage) in central region of inferior (zone 5).

4. Discussion

Our hypothesis was supported for the classic “Friar Tuck” wear pattern to the humeral head in end-stage GOA, of central and inferior cartilage damage and loss [10]. The correlation of cartilage thickness, modified Mankin Score, and OARSI score with range of motion is all consistent with more central and central-inferior cartilage damage and arthritis, and the “Friar Tuck” pattern. This pattern is also consistent with humeral head contact patterns and frequency of contact in 0–120° of arm elevation [38]. However, consistent with other reports [10], we also
identified a sub-phenotype of patients with more focal inferior cartilage wear associated with female sex, non-dominant shoulder, higher pre-operative SANE and ASES scores, greater pre-operative range of motion (external rotation and forward flexion), in both affected and contralateral shoulder, and radiographic evidence of concentric wear patterns and smaller inferior osteophytes, suggesting that end-stage primary GOA could represent convergence of a diverse set of disease sub-phenotypes.

This study was not designed to understand the causation behind the identified correlations between clinical parameters, or between clinical parameters and histological and morphometric characteristics. However, multiple variations in the normal shape, size, inclination and version of both glenoid and humeral head are reported; some of these parameters are asymmetrical bilaterally, and some have demonstrated association with sex, age, dominant vs non-dominant side, and sporting activity (Reviewed in Soames [39]). The inverse relationship between increasing patient age and lower pre-operative pain observed here is consistent with other recent work [40,41]. Regardless, the trajectory of how normal variants of humeral head and glenoid anatomy, relate to clinical variables or to the sub-phenotypes of end-stage GOA we have begun to uncover here remain understudied.

The range in cartilage thickness observed at different regions on the humeral head in the present study was substantial (Range 0—2.5 mm) and varied dramatically within the same humeral head. Humeral head cartilage thickness in normal cadaveric specimens also varies substantially by region (Range 0.44–1.5 mm) [42], and is thickest (mean ~1.1 mm) in the most central portions of the humeral head, and inferior of the periphery (mean ~1 mm). In contrast, normal cadaveric humeral head cartilage thickness is thinnest in the remainder of the periphery (Mean ~0.77–0.98 mm) [42]. This observation among non-arthritis cadavers is the opposite of the present GOA study, in which cartilage was consistently thinnest in the most central regions (Mean 0–0.25 mm) and anterior-inferior periphery (0.4–0.55 mm) and thicker in the remaining periphery (Mean 0.9–1.25 mm). Together, these findings suggest that total central humeral head cartilage loss in end-stage GOA could approximate 1.5 mm, but peripheral cartilage could thicken by almost 2 mm in some patients, particularly in superior and superior-anterior zones. This study did not allow evaluation of these changes over time, or study the causes of these changes, but previously, thickening of the exact center of the humeral head cartilage in cadavers [43], was associated with early increases in cell volume and cartilage thickness, which was then followed by decrease in cellularity and loss of cartilage. In this study, cartilage of the central portions of the humeral head was consistently thinner or absent compared to that of the periphery, consistent with the apparent GAO model novel additional predictive relationships between clinical and histopathological data, or to further separate out the apparent GAO sub-phenotypes identified, particularly given the lack of normal cadaveric control samples, but these data serve as a prelude for ongoing study.

The presence of a spectrum of pathologic changes ranging from cartilage eburnation and loss of some subchondral bone, all the way to cartilage preservation with subchondral bone plate thickening or thinning. This is consistent with previously reported findings in the humeral head [10]. Outside of these regions, in anterior, superior and posterior peripheral regions of the humeral head, increased subchondral bone area was consistently associated with increased size of inferior osteophyte. In addition, increased peripheral subchondral bone plate thickness was consistently associated with higher ASES scores and increased pre-operative range of motion. These findings could represent a biomechanical sub-phenotype of GOA not yet fully described that could be comparable to similar observations in the knee, in which osteophyte severity and localization of subchondral sclerosis are associated with specific pre-arthroplasty gait patterns in end-stage knee osteoarthritis [47].

As reported previously [36,37], there was a high degree of correlation between OARSI and modified Mankin histological scores for the central and peripheral regions of the humeral head, despite the fact they predominantly report cartilage loss and cartilage structure respectively. Both scoring systems revealed an association between less cartilage pathology peripherally and higher pre-operative external rotation in the operative shoulder, as well as an association in the superior half of the humeral head between less cartilage pathology and increased pre-operative forward flexion in both the operative and contralateral extremity. OARSI and modified Mankin scores also revealed associations between less cartilage pathology centrally or peripherally in the posterior-superior periphery of the humeral head and higher pre-operative SANE or ASES scores. While the data could suggest that shoulder conditions that limit function and range of motion result in worse GOA, this is opposite to the situation in the knee and from clinical GOA studies. In the knee, maintaining appropriate physical activity is important for joint health even in the presence of osteoarthritis [48]. Therefore the possibility exists in the shoulder that maintaining range of motion is important for preserving humeral head cartilage health, a notion supported by a number of arthroscopic studies that manage GOA by restoring range of motion [23,25,49–53] because in early GOA, joint stiffness is a bigger complaint than pain [25]. The use of capsular release as a critical part of treatment of early osteoarthritis in conjunction with partial biologic or prosthetic resurfacing [54–59] also supports the critical role for a critical interaction between preserving range of motion and joint health. The preponderance of joint stiffness rather than pain in early GOA is also consistent with our results here, in which, in contrast to the many associations of humeral head pathology with range of motion, pre-operative pain was associated only with cartilage and subchondral bone plate thinning in the periphery of anterior-inferior humeral head, and not with any outcome measure associated with cartilage pathology.

This study has several limitations: A selection bias for more severe GOA is present because all patients had previously been indicated for an anatomic total shoulder arthroplasty prior to enrolling in this study group, compared to the average patient presenting to clinic for an initial visit with GOA. The average age of patients enrolled in this study was older than that of studies describing outcomes for patients treated with arthroscopic procedures for GOA [23,49,50]. Quantitative bone morphometry data was not available in this study, nor could cartilage or subchondral bone pathology be paired with data from the glenoid or periartricular soft tissues. However, some of these data could be obtained from pre-operative imaging and micro-computed tomography techniques pre-operatively or from resected tissues moving forward. Finally, while this study was appropriately powered to describe the pattern of osteoarthritis change in these end-stage humeral heads, given the large number of variables involved, this study was under-powered to be able to model novel additional predictive relationships between clinical and histopathological data, or to further separate out the apparent GAO phenotypes identified, particularly given the lack of normal cadaveric control samples, but these data serve as a prelude for ongoing study.
5. Conclusion

We describe distinct histopathologic cartilage wear patterns in advanced GOA that predictably involve greater wear in the central compared to peripheral regions and also identify a GOA phenotype associated with more focal inferior humeral head lesions.

Author contributions

APM, DL, and GEG were involved in the conception and design of the study. APM, ZK, VABC, AC, MC, SJF, LGMF, DL and GEG were involved in acquisition of data. APM, ZK, AC, MC, LGMF, DL and GEG were involved in analysis and interpretation of data. APM, LGMF, DL and GEG drafted the article or revised it critically for important intellectual content. All authors gave final approval of the submitted version or the manuscript.

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Declaration of competing interest

No author had competing interests or conflicts of interest.

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Appendix A. Supplementary data

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