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ORIGINAL COMMUNICATION

A Cadaveric Investigation into the Links between Macroscopic and Microscopic Osteoarthritic Changes at the Hip

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Our objective was to investigate the frequency and distribution of osteoarthritic changes at the hip, including the relationship between osteoarthritic lesions on the femoral head surface and histological changes in articular cartilage, in 12 cadavers. Twelve embalmed cadavers (five males and seven females) were dissected, and the femoral head was removed from both sides (24 femoral heads). Any gross osteoarthritic changes were noted and graded (on a scale of 1–3). A circular disc was then removed from the equator of the femoral head and divided into nine regions. Out of 192 segments, 54 underwent sectioning and staining with haematoxylin and eosin to assess histological changes in cartilage. Osteoarthritis of the hip was present in all cadavers, with all males having bilateral OA and 50% having grade 2 or higher lesions (50% were grade 1), and four of the seven female specimens having bilateral OA and only 7% with grade 2 lesions (with 71% grade 1 and 21% normal). Chondrocyte clustering was most commonly observed in the deep layer of cartilage followed by the intermediate and superficial layers respectively, as the grade of the macroscopic lesion increased. Cartilage injury at the histological level precedes any visible denudation of the femoral head articular cartilage. This study supports the hypothesis that early osteoarthritic changes occur in the deep layer of cartilage near the tide mark and progress superficially concomitant with an overall increase in the osteoarthritic lesion size on the femoral head surface. Clin. Anat. 19:115–124, 2006.

Key words: osteoarthritis; orthopaedics; hip; cartilage; degeneration

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disease that affects the synovial joints. OA is relatively common with about a third of white North Americans and white Northern Europeans (men and women) aged 25–74 having features of radiographic OA involving at least one peripheral joint group (Creamer and Hochberg, 1997). Over the age of 70, up to 90% of the population have some radiological evidence of OA (Lawrence, 1977). OA is a disabling disease, which, as our society ages, becomes an increasingly important challenge to health care funding. It has been estimated that the total costs for arthritis (all types including OA) may exceed 2% of GDP (Yelin, 1998).

The true extent of OA is difficult to determine, as most studies use clinical or radiological methods to determine whether someone has OA (Lawrence, 1977; Oliveria et al., 1995; Creamer and Hochberg, 1997; Ingvarsson et al., 1999). These methods are useful but in the case of clinical studies it is difficult to allow for psychological compensation and "yeah sayers" (with respect to pain perception and symptomatology) and such studies cannot detect subclinical osteoarthritic changes. Radiological studies thus far have not permitted observation of the entire joint surface and indeed, Baage et al., reported that radiographic evidence of OA could be present without

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clinical signs and clinical signs could be present without radiographic evidence (Bagge et al., 1991). Although postmortem studies have been carried out (Doherty, 1994), these have not tended to link gross degenerative changes with those occurring at the histological level. A cadaveric-based methodology thus allows the study of very early osteoarthritic changes that are often not detected by other methods. Thus in this study, the entire femoral head surface is available for inspection and therefore more objective observation is possible.

The view that OA is a "wear and tear" disease—an inevitable consequence of ageing—has been largely replaced with the thinking that OA is a metabolically active, dynamic process, which may be triggered by a variety of insults. However, the etiology of OA is yet to be fully elucidated with research, and opinion being polarized for decades by two schools of thought (Kuettner et al., 1992; Brandt et al., 1998). One view is that OA is initiated in articular cartilage itself with an initial event leading to disequilibrium between proteoglycan and collagen components, this in turn leading to degeneration and OA (Kuettner et al., 1992; Brandt et al., 1998; McKinley and Bay, 2001; Nordin and Frankel, 2001). The other view is that an initial event leads to subchondral bone stiffening (which precedes cartilage damage) thus propagating abnormal stress gradients to articular cartilage resulting in its degeneration (Radin and Paul, 1971; Simon et al., 1972; Radin and Rose, 1986; Day et al., 2001).

This study aims to determine the true extent and distribution of osteoarthritic changes at the hip in an elderly population of cadavers and to correlate those gross degenerative changes with changes occurring at the histological level, which will provide useful insights into where early osteoarthritic changes begin and how they progress.

MATERIALS AND METHODS

Tissue Collection and Grading

The hip joints of 12 embalmed, Caucasian cadavers (age range 76–101) were dissected using a posterior approach, and the hip was forcefully dislocated using a combination of abduction and internal rotation. The 24 femoral heads were removed using a hacksaw to cut through the femoral neck. The femoral head was then placed in a standard position (where the fovea faced the experimenter), allowing for consistency in measurements, grading, and photography. Two standard photographs were taken for all specimens irrespective of pathological status: a front view (with the fovea facing the digital camera) and a superior view.

Fig. 1. A photograph of a specimen with grade 1 osteoarthritic changes.

The severity of any osteoarthritic lesion was classified as grade 1, grade 2, or grade 3 using a system developed by our department. To our knowledge, such a classification system has not been reported in the literature. The grade was determined mainly by the depth of the osteoarthritic lesion on a macroscopic view of the femoral head. A grade 1 specimen refers to an osteoarthritic lesion observed as a roughened, inconsistent area, which does not penetrate into underlying subchondral bone. Grade 2 specimens have severe osteoarthritic changes, observed as marked degeneration of the cartilage with the erosion extending into underlying subchondral bone. Grade 3 describes a specimen with generalized osteoarthritic changes covering most of the femoral head surface with a large degree of cartilage thinning (Figs. 1 and 2).

If the osteoarthritic grade for a particular specimen was not obvious, agreement with a second opinion was used to determine the final classification. Other details such as the cadaver's age, sex, and the side from which the femoral head was removed were also noted. The sample size was too small to consider a correlation between age and osteoarthritis (OA) grade.

Histological Preparation

A cross-section from the equator of each specimen was cut out using a hacksaw with the femoral neck held in a vise (with the upper limit of each section being the lower edge of the fovea). The area, which

Fig. 2. A photograph of a specimen with grade 2 degenerative changes.

was previously just below the fovea, was then marked and acted as a fixed reference point. From this hemi-section, a 5-mm-thick cylindrical disc was formed by sawing 5 mm inferior to the superior edge of the hemi-section using a band saw (where the margin was set to 5 mm). The discs were divided into nine regions (resulting in $9 \times 24 = 216$ segments) using a hacksaw and vise, with each region of the disc being classified according to its position relative to the reference point described earlier (area 2 in Fig. 3).

The whole segment was processed histologically apart from segment 5, which was purely a trabecular bone with no cartilaginous borders (thus $216 - 24 = 192$). This system would allow the origin of any segment (in terms of its position in the femoral head) to be ascertained and allow for a more detailed analysis to be made from the histology. When each segment had been cut, it was placed in formaldehyde preservative. Each of these segments was then prepared for histology by first undergoing demineralization with formic acid (made up from 900 ml of 10% formaldehyde and 100 ml of 90% formic acid). Once demineralization was complete (2 weeks), specimens were washed with distilled water and placed in small porous containers with 70% alcohol for dehydration overnight, following which they were bathed in chloroform (used as a mordant) for two days in a fume cupboard. The containers were then filled with molten wax, thus embedding the specimens. When the wax blocks had cooled, they were placed in ice and sectioned using a microtome set at 6 μm, with subsequent staining using haematoxylin and alcoholic eosin and observation through a standard light microscope.

The histological analysis examined the differences between segments from normal and grades 1, 2, and 3 specimens in terms of cartilage thickness, fibrillation, tide mark irregularity, and the presence of chondrocyte clustering (a cluster being defined as >2 cells per chondron) in any of the three cartilage layers (deep, middle, and superficial and excluding the zone of calcified cartilage). These findings have been classed as indicators of osteoarthritic change.[9,11,16] The cartilage thickness was measured using a graduated eyepiece, while cartilage fibrillation, chondrocyte clustering, and tide mark regularity were classed as present or not.

Statistical Methods

A χ^2 test was used when there were two independent groups of individuals and one wanted to know if the proportions of individuals with a characteristic are the same in the two groups (Bland, 2000). The data was put into a 2×2 contingency table with observed values from the sample and expected values (from the null hypothesis) for the variable under investigation, for the two groups (Petrie and Sabin, 2000). The χ^2 values are then added up and the P-value is obtained from the χ^2 distribution for (in the case of a 2×2 table) one degree of

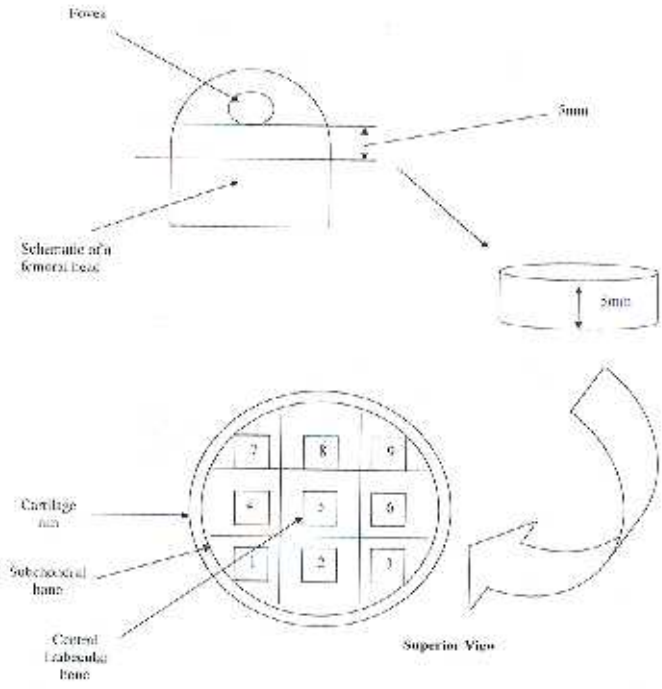

Fig. 3. A diagram showing the production and classification of different areas of the disc.

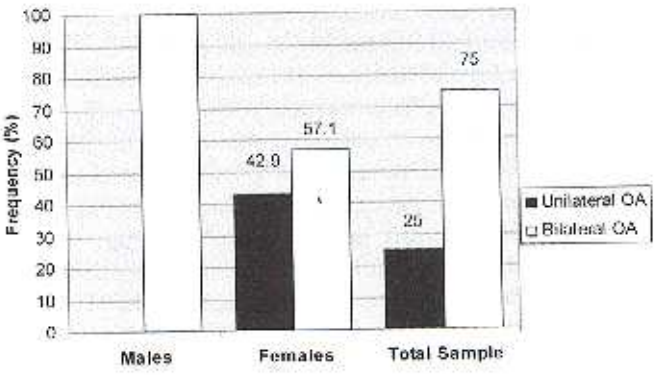

Fig. 4. Frequency of osteoarthritis among the 24 femoral heads (10 male and 14 female).

freedom. The frequency n in any one cell has to be 5 or more for the test to be valid. If n was less than 5 for any cell, then Fisher's exact test was applied to obtain a P-value that does not rely on the approximation to the χ^2 distribution (Petrie and Sabin, 2000). An unpaired, 2-tailed t test was used when there were two independent (unrelated) groups of individuals and one variable of interest. It was assumed in the population that the variable is normally distributed and the variances of the two groups are the same.

RESULTS

Gross Morphology

All cadavers showed either unilateral or bilateral degenerative changes. Combining right and left sides, the frequency of OA among the 24 femoral heads was 87.5% (21/24, see Fig. 5). Eleven of the 14 female femoral heads had OA (78.6%) and three of the seven female cadavers (42.9%) had unilateral OA (four out of seven were thus bilateral), whereas all male cadavers had bilateral OA (see Figs. 4 and 5). The frequency of OA and the percentage of bilateral cases among males were significantly higher than that for females ($P < 0.01$, Fisher's exact test). The difference in the frequency and severity of OA on the left and right sides was not statistically significant, and there were no significant age-related differences in the frequency of OA. There are significantly more male grade 2 specimens ($P < 0.01$, Fisher's exact test), and the single grade 3 specimen was also from the left side of a male cadaver. The graphs show the frequency, distribution, and grading of OA in male and female femoral heads.

Histology

Of the 216 segments, 192 have a cartilaginous boundary (216 − 24, relating to segment 5). Out of the 192 segments, 54 (28.1%) underwent histology. To allow for a meaningful analysis each of the specimens was grouped according to their grade.

In Table 1, n refers to the total number of segments in that category; for example, $n = 4$ for grade 3 means that the histological information is based on four different segments from the same single grade 3 specimen, whereas for grade 1, where $n = 29$, this comprises 29 segments from nine different grade 1 specimens. Generally, with the onset and progression of OA (i.e. as the grade of the specimen increases), there is a decrease in cartilage thickness, an increase in the frequency of cartilage fibrillation and irregular tide marks, and an increase in the frequency of chondrocyte clustering in the middle and superficial cartilage layers (with clustering in the deep layer identified in 83.3% of segments, this was differentiated from disorganized column orientation).

Cartilage Thickness

The difference between normal and grade 1 or grade 2 specimens was not statistically significant, but grade 3 segments showing changes had significantly thinner cartilage than other specimen groups ($P < 0.01$, unpaired t test). The cartilage thickness of grade 1 specimens was significantly greater than that of grade 2 and grade 3 specimens ($P < 0.01$) and non-significantly greater than that of normal (Fig. 6).

Figure 7 shows that there is a more uniform decrease in cartilage thickness (i.e. across different segment positions) in grade 3 specimens. However, normal, grade 1, and 2 specimens show more variation in thickness across different segment positions (Fig. 8).

Cartilage Fibrillation

Figure 9 shows that grade 2 and grade 3 specimens had a significantly greater frequency of cartilage fibrillation than that in grade 1 specimens ($P <$

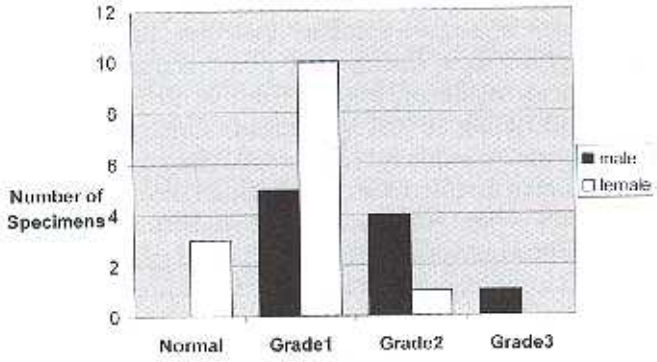

Fig. 5. The number of normal, grade 1, 2, and 3 specimens for males and females.

TABLE 1. Histological Results According to Grade

Specimen type	Average cartilage thickness (mm)	Fibrillation present (%)	Irregular tide marks present (%)	Chondrocyte clustering		
				Deep layer (%)	Middle layer (%)	Superficial layer (%)
Normal ($n = 6$)	0.79	0	0	66.7	33.3	0
Grade 1 ($n = 29$)	0.89	10.3	42.3	86.2	62.1	20.7
Grade 2 ($n = 15$)	0.72	53.3	100	80	80	26.7
Grade 3 ($n = 4$)	0.41	100	100	100	100	100

0.01, χ^2 test), with no normal segments showing evidence of cartilage fibrillation. Normal and fibrillated cartilage specimens are shown later for comparison.

Tide Mark

Grade 2 and grade 3 specimens had a significantly greater frequency of irregular tide marks than that in grade 1 specimens ($P < 0.01$, χ^2 test) (Fig. 10). There were no segments from "normal" specimens with irregular tide marks (Figs. 11 and 12).

Figure 11 shows a specimen with grade 1 osteoarthritic changes, and the tide mark for this specimen is regular tide mark. In some cases (as shown in the grade 2 specimen), the tide mark was doubled and irregular (Fig. 12).

Chondrocyte Clustering

Chondrocyte clustering (>2 cells per chondron) occurred in all cartilage layers, but in general, the deep layer showed more clustering than the intermediate layer, which in turn showed a greater frequency than the superficial layer. Clustering in all layers correlated with the grade of OA (Fig. 13).

Figure 14 compares the degree of chondrocyte clustering in each cartilage layer for normal and grade 1, 2, and 3 specimens (where 300% equates to the presence of chondrocyte clustering in all three layers). The overall extent of clustering in the three layers was significantly greater for grade 3 specimens when compared with all other grades ($P < 0.01$, χ^2 test). Grade 1 specimens had significantly more chondrocyte clustering than normal specimens ($P < 0.01$, χ^2 test). The normal specimens also showed significantly less clustering in the intermediate layer than that of grade 1, 2, and 3 specimens ($P < 0.01$, χ^2 test). Normal specimens did not have any clustering in the superficial layer. Grade 3 specimens had a significantly greater degree of clustering than that of grade 1 and 2 specimens in the superficial layer ($P < 0.01$, χ^2 test).

The greatest progression or increase in chondrocyte clustering takes place between normal and grade 1 specimens and between grade 2 and grade 3 specimens. Well-developed osteophytes were only seen in the single grade 3 specimen, with early osteophyte formation in some grade 2 specimens.

DISCUSSION

Every cadaver had evidence of osteoarthritic changes, either unilateral or bilateral. This 100% prevalence among the cadavers is significantly greater than the 35.4% prevalence reported by Ingvarsson et al. (1999) in people aged 85 and above. Most epidemiological studies have used radiological or clinical findings to determine the presence of OA, while in the present study, OA was determined by a visual classification of degenerative changes on the entire femoral head surface, this may account for the

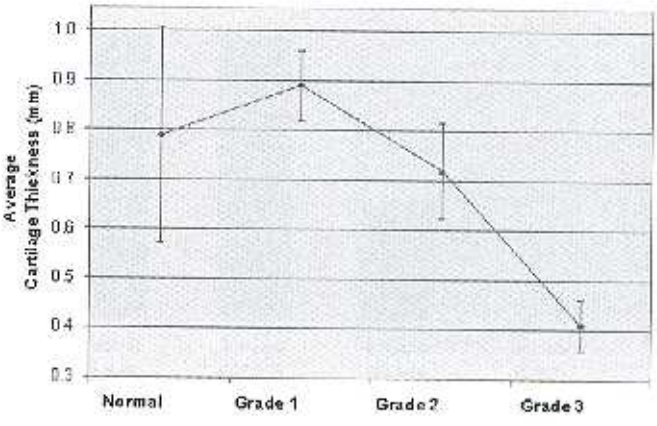

Fig. 6. Cartilage thickness against specimen grade.

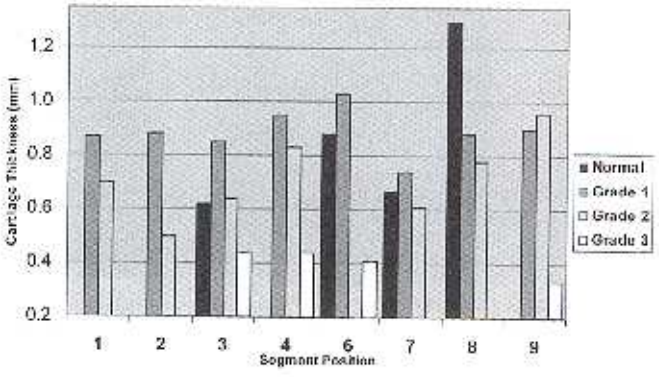

Fig. 7. Cartilage thickness against segment position.

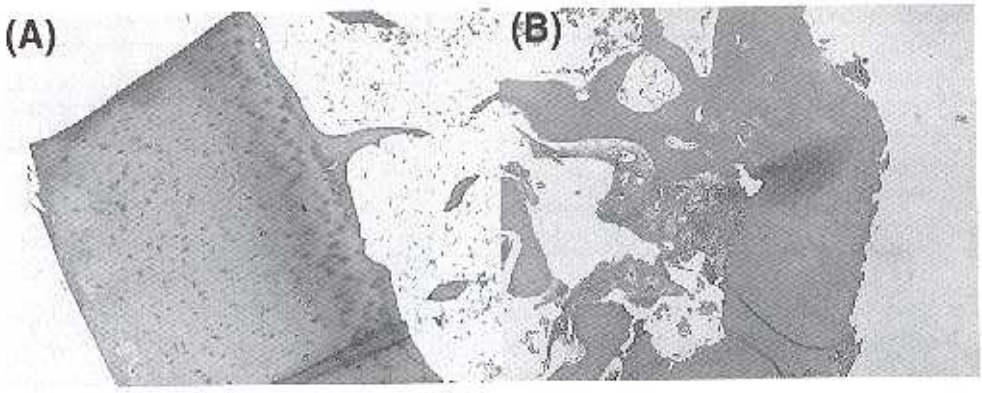

Fig. 8. A, B: A normal cartilage surface and thickness in a grade 1 OA specimen on the left (specimen D left side, segment 4 – x50), with cartilage fibrillation and thinning in the grade 3 specimen on the right (specimen C left side, segment 3 x50). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

disparity. However, these results are similar to some autopsy-based studies, which have used similar methods and found almost universal degenerative changes in people above 65 years (Doherty, 1994). The high prevalence rate in this study would result from a combination of methodology and the age-range being studied.

Significantly, more males than females showed degenerative changes and of a more sever nature (with 50% of femoral heads from males being classed as grade 2 when compared with 7% for femoral heads from female cadavers). Doherty (1994) reported that females have a greater prevalence of hip OA after the age of 70, whereas males have a greater prevalence of hip OA below age 60. These results are also consistent from a biomechanical point of view as the joint reaction force at the hip is greater in men than in women because of the greater angle of inclination in males (Ozkaya and Nordin, 1991). This may also partly account for the greater severity of OA among males.

The results from histology suggest that certain indicators of cartilage damage and OA such as a decreased cartilage thickness and cartilage fibrillation are relatively late events in the pathogenesis of OA, reaching a significant frequency only when the osteoarthritic lesion on the femoral head surface was already advanced (being grade 2 or 3). Prior to cartilage thinning, there appears to be an initial increase in cartilage thickness (see Fig. 6). Although this was shown to be a nonsignificant trend (possibly because of the low number of "normal" samples), this pattern of degenerative change is similar to that observed by Panula et al. (1998), where cartilage thickness increased prior to surface fibrillation, which may reflect an initial hypertrophic response (increased matrix production) by chondrocytes in response to injury or excessive force transmission (Panula et al., 1998).

The frequency of irregular tide marks increased rapidly between normal and grade 1 specimens and between grade 1 and grade 2 specimens, suggesting irregular tide marks increase in frequency earlier than cartilage fibrillation and cartilage thinning, which become significant only in grade 2 and 3 specimens. The main function of the tide mark is to act as a fluid barrier between the zone of calcified cartilage (and underlying subchondral bone) and the deep layer of cartilage (Ogata and Whiteside, 1979; Adams et al., 2002). Disruption of this layer may lead to fluid trans-

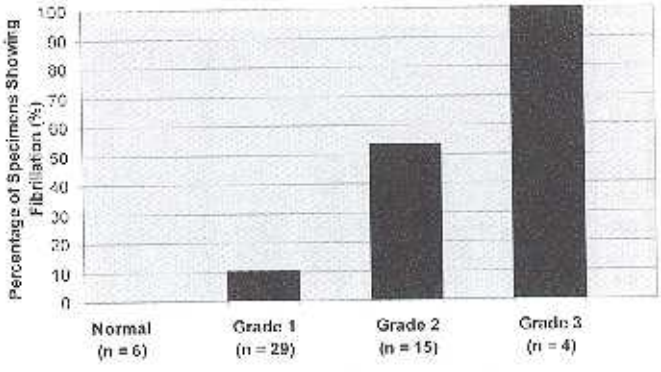

Fig. 9. The frequency of cartilage fibrillation for normal, grade 1, 2, and 3 specimens.

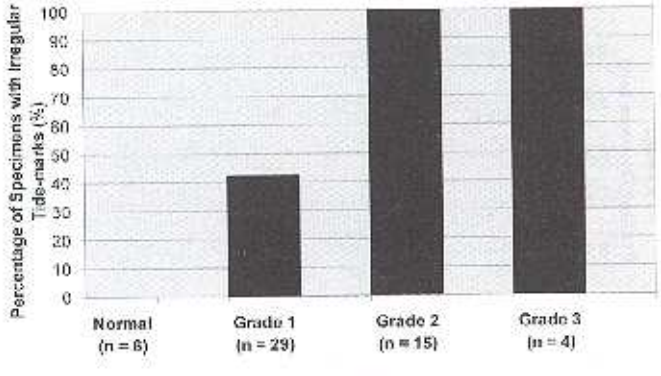

Fig. 10. The frequency of irregular tide marks for normal, grade 1, 2, and 3 specimens.

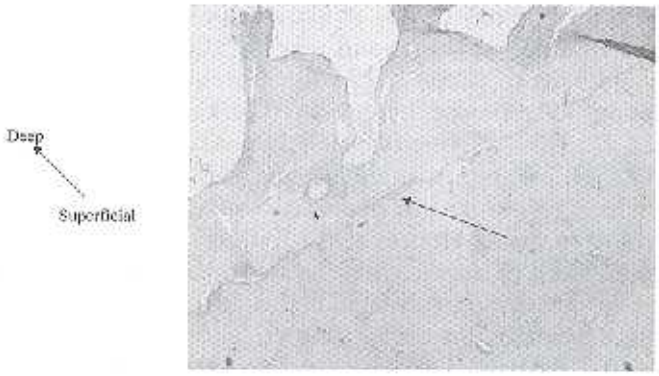

Fig. 11. A regular tide mark seen in a specimen, right side, segment 9 (×100). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

fer between cartilage and bone. Conceivably, the altered dynamics and forces in the area could cause a reactive hypertrophy and division of the chondrocyres in the vicinity, leading to chondrocyte clustering and cartilage thickening. Referring to Figures 13A and 13B, one can see how the chondrocytes in Figure 14 have greater intercellular spacing.

Revascularization of the deep layer of cartilage by vessels from subchondral bone, which penetrate the tide mark, has also been reported (Kuettner and Pauli, 1983). Fenwick et al stated that osteoarthritic cartilage (but not non-OA cartilage) showed invasion by blood vessels from a chorioallantoic membrane, with loss of staining for proteoglycans and cartilage specific glycosaminoglycans (Fenwick et al., 1999; Nikolaeva et al., 2002). Such changes in composition could alter the fluid flow within cartilage, and therefore, its compressive strength and shear modulus – with several recent studies reporting such altered biomechanical dynamics in response to increased water content and decreased proteoglycan content of cartilage (Kerin et al., 1998; Burton-Wurster, 1999; Treppo et al., 2000; Nikolaeva et al., 2002; Appleyard et al., 2003). More recently, loss of immunotolerance to a cartilage protein specific to the intermediate layer was reported in the context of OA (Tsuruha et al., 2001). These reports emphasize the potential importance of the tide mark in the etiology and progression of OA.

Chondrocyte clustering is believed to be indicative of cartilage injury (Wayne et al., 2001). It was observed in all layers, but only normal specimens showed no chondrocyte clustering in the superficial layer and significantly lower levels of clustering in the intermediate layer. Overall, clustering gradually increased with grade and was generally most common in the deep layer, followed by the intermediate and superficial layers, respectively. Only the grade 3 specimen showed maximum clustering in all three layers, and in all the segment positions analyzed, this is in accordance with the severity of the observed lesion on the femoral head surface. Chondrocyte clustering in the normal specimens may indicate early osteoarthritic changes (with column organization being spared). However, no lesion was seen on the femoral head surface and no tidemark changes were observed, implying that early osteoarthritic changes may take place in the deep layer of cartilage (although such chondrocyte clustering may not necessarily relate to an osteoarthritic process), a finding that is further supported by the early increase in tide mark irregulariry, and has previously been linked to the pathogenic mechanism of OA (Kuettner et al., 1992). The formarion of osteophytes is also a relatively late event in the pathological range studied. These findings suggest that osteoarthritic progression at the histological level follows a temporal sequence (Fig. 15).

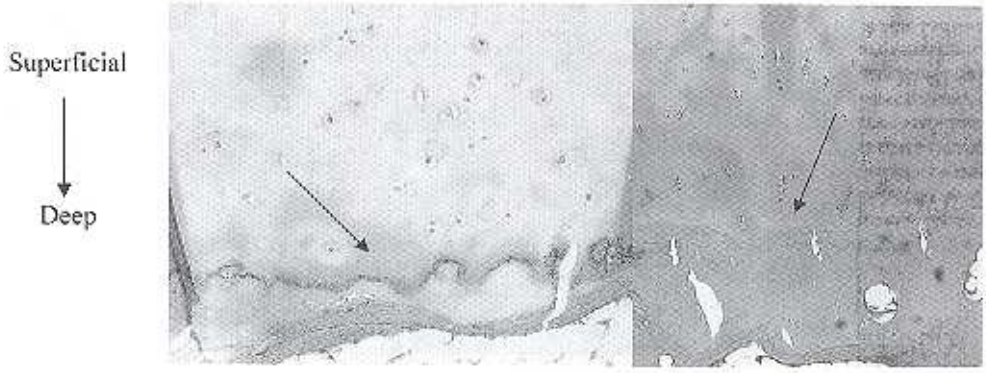

Fig. 12. Doubled irregular tide marks seen in a specimen right side, segment 2 and segment 9, respectively (×200 and ×100, respectively). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

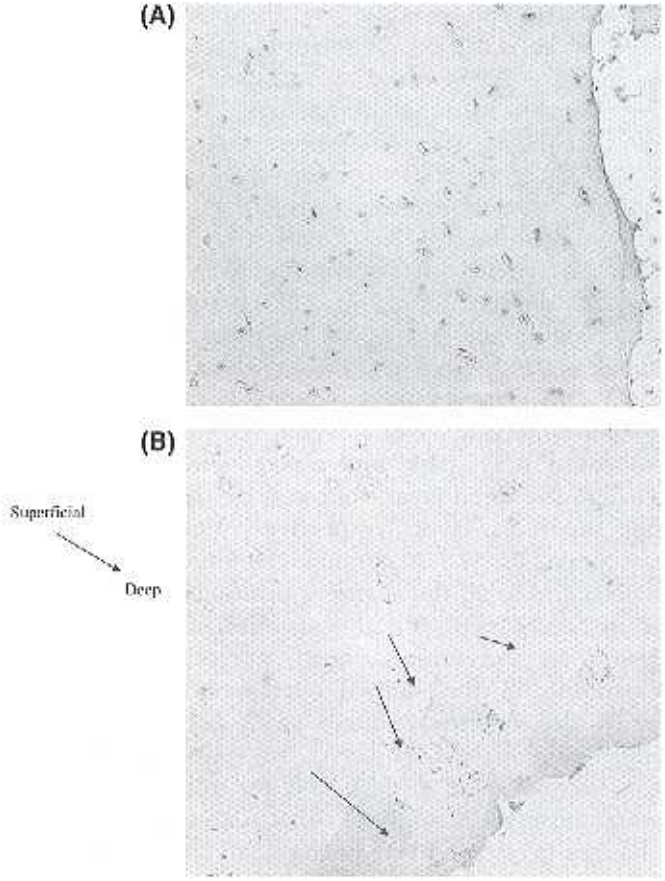

Fig. 13. A: "Normal" cartilage with no evidence of chondrocyte clustering (×100). B: "Articular" Cartilage with evidence of chondrocyte clustering (×100). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The findings of this study do not support a gradual thinning or "wear and tear" of the cartilage from superficial to deep layers with subsequent damage to bone, as reported by others (Clarke, 1971; Saxena et al., 1991; Doherty, 1994; Panula et al., 1998). Rather, it supports the view that early changes occur in the region of the deep layer of cartilage nearest the tide mark. Hence, these findings indirectly support more of an interplay between cartilage and the zone of calcified cartilage at the tide mark with perhaps changes on either side triggering the osteoarthritic process. The results of this study would also be more consistent with the hypothesis of subchondral bone stiffening predisposing overlying cartilage to degenerative change through the propagation of abnormal force gradients (Simon et al., 1972; Bailey and Mansell, 1997; Day et al., 2001). These force gradients are likely to be sharpest at the region of the zone of calcified cartilage, the tide mark, and the deep layer of cartilage, as this is the interface between hard and soft tissues and consequently the potential triggering point for the osteoarthritic process if the right "mix" of etiological factors is present.

It has been over 30 years since Mankin et al. documented the heterogeneous changes in cartilage brought on by the Osteoarthritic process (Harrison et al., 1953; Ferguson, 1964; Goodfellow and Bullough, 1967; Sokoloff, 1969; Mankin et al., 1971). There is now an increasing need for further study that correlates macroscopic findings with histological changes, with the aim of gaining fresh insights into

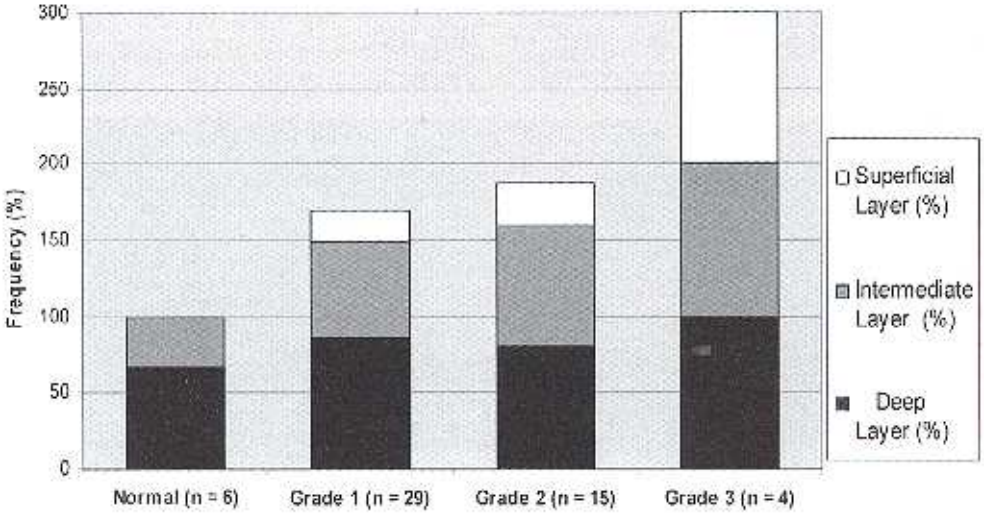

Fig. 14. The frequency of chondrocyte clustering in the different cartilage layers (300% indicates maximum clustering in all three layers).

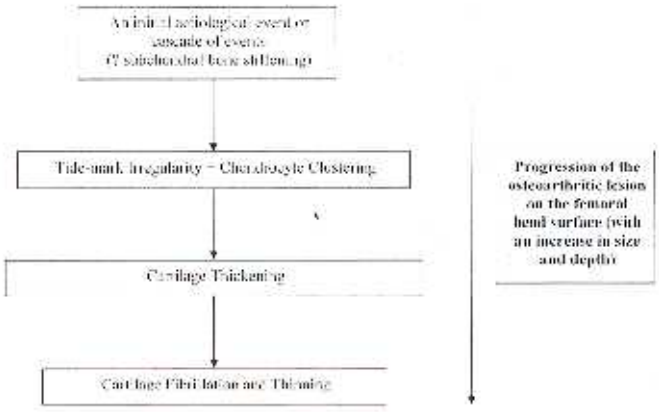

Fig. 15. A proposed temporal sequence for histological changes in cartilage.

the etiology of OA, which to this day is somewhat of an enigma. Furthermore, there is a need to extend the pathological spectrum seen here to those with more severe OA (beyond grade 3 severity—ideally those removed in total hip replacement for hip OA). These cartilage changes should ideally be analyzed together with changes in other joint components, which are also involved in the pathology of OA, such as the subchondral and trabecular bone, the synovium, the joint capsule, and the ligaments. Studies are increasingly showing that OA is a disease of the whole diarthrodial joint not just the cartilage or the bone, and there may be multiple points of initiation for the disease process (Bailey and Mansell, 1997; Day et al., 2001; McKinley and Bay, 2001; Muehleman et al., 2002).

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