

EXTENDED REPORTS

Distribution of distal femoral osteophytes in a human skeletal population

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Abstract

Objectives—To examine objectively spatial patterns of osteophytes around the distal end of the femur and to identify distinct subgroups.

Methods—A sample of 107 human femora from a large skeletal population were selected for study. These femora included subjects with evidence of late stage osteoarthritis (that is, with eburnation present) and those with no such evidence. The location of osteophytes was recorded using a video camera and digitised computer images were extracted. Multidimensional scaling was used to identify clusters of femora based upon osteophyte location.

Results—A distinct subgroup of femora was identified with osteophytes present only within the intercondylar notch region. None of these subjects had any evidence of eburnation.

Conclusions—This finding adds to an earlier study based on radiographs. Osteophytes located within the intercondylar notch of the femur appear to be a distinct subset, which may occur either as an early stage of knee osteoarthritis or for some independent reason.

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Osteoarthritis (OA) of the knee is a common, painful, and debilitating condition. It affects up to 30% of Western populations over the age of 65¹ and presents a large burden for the health-care services.²

OA is characterised radiographically by loss of joint space (indicative of focal cartilage loss), subchondral sclerosis, bony contour remodelling, and the presence of osteophytes. The cause of OA is poorly understood. It is heterogeneous with many distinct causal pathways,³ and the concept of OA as a single disease entity has been rejected by some, leading to the use of the phrase “osteoarthritic disorders”.⁴

There have been attempts to distinguish types of OA based upon the anatomical location of constituent features. Several studies have sought to describe subgroups of OA within the hip^{5,6} and within the knee, particularly making a distinction between OA of the patellofemoral joint (PFJ) and OA of the tibiofemoral joint (TFJ).^{7–9}

The presence of osteophytes has commonly been used in the definition of OA. Early pathological studies distinguished OA from rheumatoid arthritis based upon the presence of osteophytes and bone remodelling,¹⁰ and more recent radiographic based definitions have depended on the definite presence of osteophytes.^{11–13} However, it has been shown that osteophytes within the knee joint are not necessarily indicative of other features of OA.¹⁴ Osteophytes can occur independently of knee symptoms and appear to be an age related phenomenon.¹⁵ Osteophyte formation has been shown empirically to be related to enthesophyte formation,¹⁶ suggesting that the degree to which people form new bone is at least partially dependent on systemic factors and varies considerably from one person to another.

Given the heterogeneity of OA and potential heterogeneity of osteophytes, an investigation of spatial patterns of osteophytes within joints may either provide identifications of subgroups of OA or detect osteophytic patterns that are distinct from OA.

The distribution of osteophytes within the knee joint was described by Kindynis *et al.*¹⁷ This study, believed to be the first study to examine the distribution of knee joint osteophytes, was based upon an OA group and a crystal deposition disease group using tunnel view, anteroposterior, and lateral radiographs. Marginal osteophytes were found within the intercondylar notch of nearly all those subjects with OA. Lone medial intercondylar osteophytes occurred in 27% of the femora studied. These findings, although cross sectional and based upon a subjective quantification of osteophytes, led the investigators to conclude that marginal osteophytes around the intercondylar notch are an early sign of knee OA.

In a more recent study¹⁸ Wada *et al* investigated the intercondylar notch using cadaveric knees. These investigators concluded that osteophyte growth around the intercondylar notch region correlated with the progression of medial compartment OA.

Skeletal material lends itself well to the study of OA.¹⁹ Areas of full thickness cartilage loss are shown by polished areas of bone known as “eburnation”. Osteophytes are readily seen. Small and subtle regions of osteophytosis, often not evident on radiographs, can be picked up from dry bone.²⁰ We have sought to use skeletal material and an objective data capture

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Figure 1 Example of colour coded bitmap. Red = osteophytes; blue = eburnation; yellow = damage.

method coupled with multivariate analytic methods to investigate the distribution of osteophytes around the distal femur. We hoped this approach would avoid the loss of information that occurs when subjective quantification systems using a limited number of categories to capture spatial information are applied to radiographs.

Material and methods

The study material consisted of a sample of adult femora taken from a large skeletal collection (about 2000 adult subjects) excavated from St Peter's Church, Barton-on-Humber, in the north of England. This sample was originally drawn for a study of distal femoral shape and has been described in detail elsewhere.²¹ Briefly, an attempt was made to identify every subject with eburnation of the distal femur and seek, for each, two controls matched for age and sex. Twenty three subjects had distal eburnation on at least one femur. A pool of subjects with no evidence of OA, at any site, was identified. From this pool, 46 subjects were selected as controls. Owing to missing femora, this selection resulted in 31 eburnated femora (3 in the medial TFJ region, 3 in the medial PFJ region, 23 in the lateral PFJ region, 1 in both the medial PFJ and TFJ regions, and 1 in the lateral PFJ and medial TFJ regions) and 90 non-eburnated femora. Of these 121 femora, osteophytes were present in 107— all of those with eburnation and 76 without.

Standard anthropological techniques were used for age and sex determination.²² For the purposes of this study, subjects have been aged either as over 45 years at death or under 45 years.

DATA CAPTURE

The capture of the data has been described and illustrated elsewhere²¹ and is briefly described here. The distal end of each femur, viewed axially, was filmed using a video camera fixed on a horizontal surface. The femora were placed on this surface and allowed to rest naturally upon the posterior aspects of the femoral condyles at the distal end and the greater trochanter at the proximal end. Each femur was rotated in the horizontal plane until the articular surface was parallel with the plane of the camera lens. Black and white bitmap images (576×768 pixels in size) were created by digitising the video film. All left femora were reflected to produce "right" images so that the left side of any image indicates the lateral side and the right side the medial.

Using standard PC software each bitmap was colour coded. While viewing the original bones directly, areas of osteophytes were indicated in red, bone was indicated as white, damaged bone as yellow, eburnated bone as blue, and the background was coloured black. Damaged bone edges were indicated in cyan. These colour coded images were then cropped to 128 pixel square images. Figure 1 shows an example. These were in turn converted to square numeric matrices. Each matrix entry corresponded to an image pixel and indicated, numerically, the colour of that pixel. Thus spatial information pertaining to osteophytes, bone, etc was captured numerically in a collection of 128×128 matrices.

STATISTICAL METHODS

Multidimensional scaling (MDS) was applied to this dataset. MDS is a standard multivariate technique and descriptions can be found in standard textbooks.²³ Working only from observed dissimilarities between objects, MDS constructs a low dimensional configuration of points. The interpoint distances in the configuration match, as far as possible, the given inter-object dissimilarities. Ideally, the configuration would be in two, or possibly three, dimensions so that a graphical representation of the objects can be drawn. However, it is unlikely that a large number of objects can be represented in such a small number of dimensions while retaining a perfect matching between interpoint distance and interobject dissimilarity. Therefore, the distances usually only approximate the dissimilarities. A statistic known as STRESS,²⁴ usually expressed as a percentage, can be used to judge the degree of approximation. A low value, less than 2.5% say, indicates an excellent approximation, less than 10% a fair fit, and greater than 20% a poor one.

The configuration may contain clusters of points identifying groupings of similar objects. In this study, MDS was used to seek subgroups of femora based upon osteophyte distribution. The advantage of using an MDS is that no absolute quantification of osteophyte location is required but only of the difference between femora.

To implement MDS, dissimilarities between femora needed to be defined based upon the location of osteophytes. This definition has

Table 1 Age and sex distribution of 107 femora used for multidimensional scaling

	Eburnated (n=31)	Non-eburnated (n=76)	Total
Sex			
Male	12	32	44
Female	18	42	60
Unknown	1	2	3
Age			
<45	0	4	4
>45	14	60	74
Unknown	17	12	29

Table 2 Multidimensional scaling of osteophyte dissimilarity matrix. STRESS statistics for an increasing number of dimensions

Damaged bones included		Damaged bones not included	
Number of dimensions	STRESS (%)	Number of dimensions	STRESS (%)
2	10.7	2	8.7
3	6.9	3	6.0
4	5.0	4	4.6
5	3.9	5	3.5
6	3.3	6	3.0

been described in detail²³ and is outlined in the appendix. It is calculated by aligning each pair of images as closely as possible by vertical and horizontal translation and then finding the number of common and disparate pixels. A non-metric MDS was used.²⁴

A hierarchical cluster analysis, using average linkage, was also carried out using these dissimilarity data. A comparison was made of the clusters identified using this method and those seen visually using MDS.

All analyses were carried out in SAS, version 6.12, through the MDS and cluster procedures.

Results

Preliminary MDS results suggested that inclusion of non-osteophytic femora produced a polarised configuration of just two clusters—those with osteophytes and those without. Therefore, attention was given only to those 107 femora with osteophytes. Table 1 gives the age and sex distributions of these 107 femora. The distributions were similar within eburnated and non-eburnated femora.

MDS was performed both on the full set of 107 femora with osteophytes and on the subset of 81 obtained by disregarding those with post-mortem damage. In both cases the size of the STRESS statistic, presented in table 2, indicated that a configuration in three dimensions would be more appropriate than two, but there seemed little benefit in adding a fourth dimension.

The configurations produced using the two groups of femora appeared similar, suggesting that the damaged bones had little influence on the construction of the MDS configuration. Attention has been focused on the group of 107 femora, including those with postmortem damage.

Figure 2 shows the three dimensional configuration. From this it is possible to identify two distinct groups (labelled 'A' and 'B'). To explore the nature of these groups the configuration was projected into two dimensions and re-examined. Those femora with eburnation have been identified on these figures.

Figure 3A shows the configuration projected into dimensions 1 and 2. Figure 3B shows individual femora from identified regions of the plot in 3A. A very densely packed cluster, labelled 'A' is easily identifiable. This group consists of femora with large, widespread osteophytes around the entire joint margin. Further femora "fan-out" from this region. This tight cluster together with the "fan" make up the group labelled 'A' in figure 2. All the eburnated femora lie within this group. Progressively smaller regions of osteophytes are observed in femora located progressively further along dimension 1 towards the positive end.

At the extreme values of dimension 2 are femora with osteophytes on either the lateral or marginal joint margins and no osteophytes within the intercondylar notch region. At the positive extreme, labelled 'B', is a femur with a thin, small region of osteophytes located on the medial margin, towards the anterior, with no osteophytes elsewhere. At the negative extreme, labelled 'C', is a femur with a thin

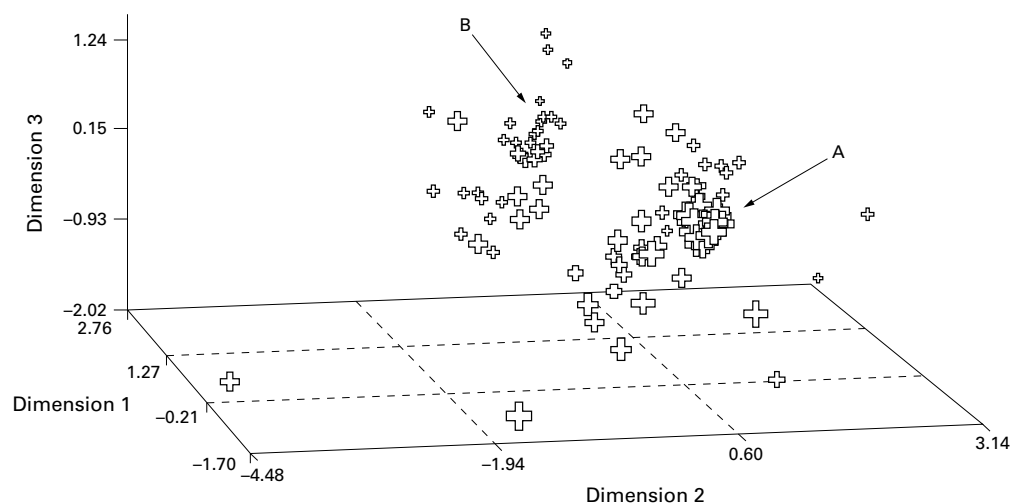


Figure 2 Configuration of femora in three dimensions. Smaller crosses indicate higher scores in all three dimensions (that is, further from the "viewpoint").

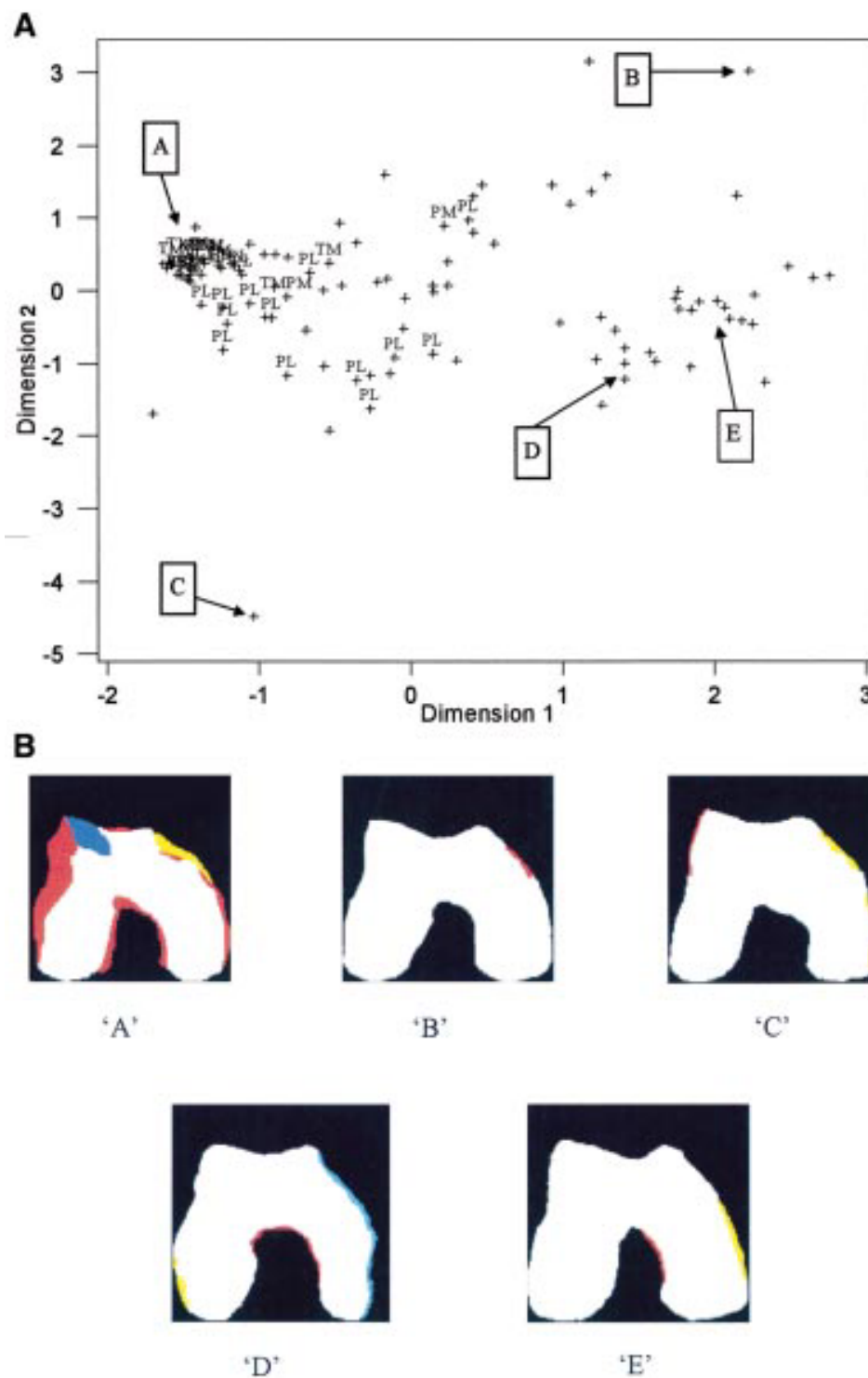


Figure 3 (A) Configuration of femora with osteophytes in dimensions 1 and 2—all osteophytic femora. PL = lateral patellofemoral eburation; PM = medial patellofemoral eburation; TM = medial tibiofemoral eburation. (B) Examples of femora from regions 'A' to 'E' identified from the multidimensional scaling—configuration projected into dimensions 1 and 2.

ribbon of osteophytes on the lateral joint margin, again towards the anterior of the bone and nowhere else.

A large cluster, distinct from the above group is located towards the extreme positive end of dimension 1. This large group, of 26 femora, is labelled 'D' and 'E' and is the second group identified in fig 4 and labelled 'B'. Members of

this group have relatively small regions of osteophytes that are located solely within the intercondylar notch region and nowhere else (in contrast with those on the extremes of dimension 2). Two subgroups have been highlighted. Those around the label 'D' had osteophytes located symmetrically on the medial and lateral sides of the intercondylar notch.

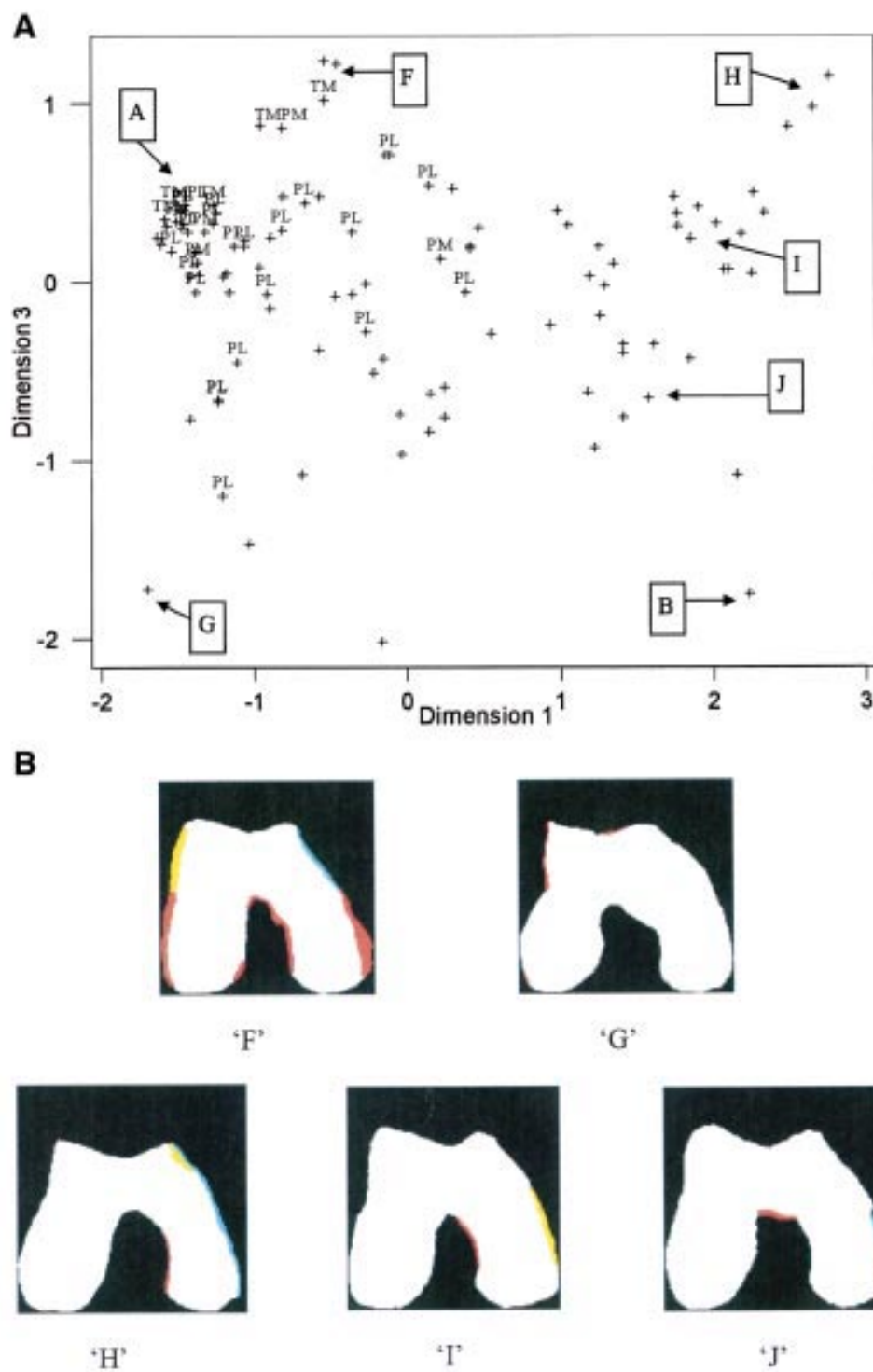


Figure 4 (A) Configuration of femora with osteophytes in dimensions 1 and 3— all osteophytic femora. PL = lateral patellofemoral eburation; PM = medial patellofemoral eburation; TM = medial tibiofemoral eburation. (B) Examples of femora from regions 'F' to 'J' identified from the multidimensional scaling—configuration projected into dimensions 1 and 3.

Femora around label 'E' had osteophytes located only on the medial side of the intercondylar notch. No eburnated femora fell into either of these two subgroups.

Figure 4A shows the configuration projected into dimensions 1 and 3. Individual femora from different regions are identified in fig 4B.

The tight cluster seen in fig 3A is still very apparent (labelled 'A'). Femora at the extremes of dimension 3 tended to have osteophytes located either towards the posterior of the bone (at the positive extreme of dimension 3) or towards the anterior (at the negative extreme, and less common).

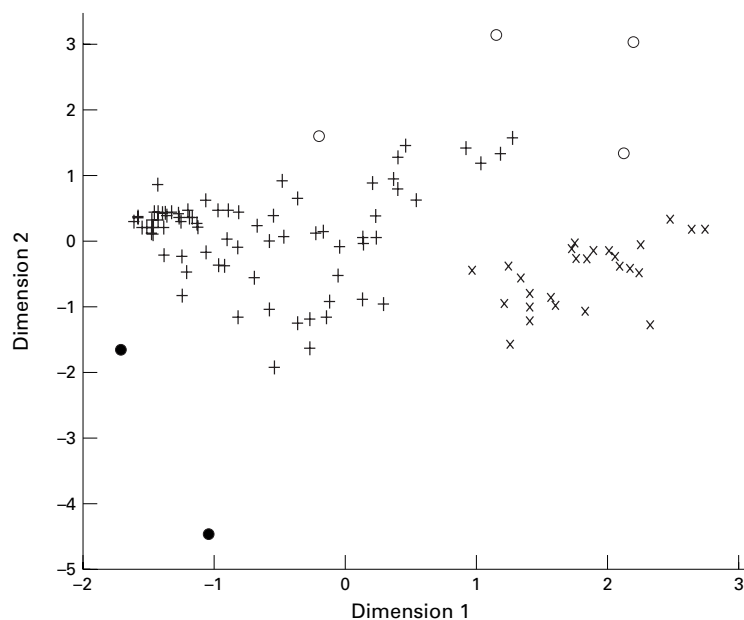


Figure 5 Configuration of femora with osteophytes in dimensions 1 and 2 (all osteophytic femora) with indication of cluster membership. Different symbols indicate four different clusters. Femora identified with 'x' have lone intercondylar notch osteophytes and form a distinct cluster from the cluster analysis.

Femora around label 'F' had large amounts of osteophytes located towards the posterior of the bone. In contrast, the femur labelled 'G' had osteophytes only around the lateral anterior joint margin and the femur labelled 'B' (the same femur labelled 'B' in fig 3A) had only a small region of osteophytes on the medial edge towards the anterior of the bone. The femora with lone intercondylar notch osteophytes are located in the regions labelled 'H', 'I', and 'J'. Those around the label 'H' had osteophytes predominantly towards the posterior of the intercondylar notch; those further towards the label 'J' had osteophytes only towards the anterior of the notch.

The cluster analysis produced groupings entirely consistent with those identified visually. Figure 5 illustrates an amalgamation of femora into four clusters using average linkage. A different symbol is used to identify each cluster. Those femora with lone intercondylar notch osteophytes fall into a distinct cluster.

From an examination of these configurations there did not appear to be any relation between the location of eburnation and location of osteophytes, other than the fact that no femur with lone intercondylar notch osteophytes had eburnation present. The degree of osteophytosis in the eburnated femora was much greater than that in the non-eburnated femora and

tended to be widespread around the joint margin. All but one eburnated femur had osteophytes within the intercondylar notch.

Femora within the identified lone intercondylar osteophyte subgroup were compared for age and sex with the remaining osteophytic femora. Table 3 shows the results obtained. There was no evidence of a relation between this subgroup and age, though only four femora came from subjects in the younger age group (that is, under 45), making any conclusions difficult. There is weak evidence of an association between sex and membership of the subgroup. The number of males relative to females is greater within this subgroup (58% *v* 42%) than within the remaining osteophytic femora (37% *v* 63%). This difference was near statistical significance at the 5% level.

Discussion

Osteoarthritis is a heterogeneous condition. Several previous studies have investigated patterns of OA and sought to classify subgroups based on the anatomical location of constituent features seen on x rays. The objective of this study was to investigate spatial patterns of osteophytes and identify subgroups of femora accordingly. Objective methods of data capture and analysis were employed, as far as possible, to avoid loss of information and any results and conclusions prejudiced by preconceived beliefs and expectations.

Although the data capture and analysis methods did not rely upon a subjective categorisation of osteophyte location from radiographs, there are still possible sources of error. The alignment of each femur to the camera might have varied, resulting in spurious variation in the anatomical location of osteophytes. The colour coding of these regions might have been another source of error. Although coded with direct reference to the original bone, it is possible that some smaller regions were missed or not reproduced accurately on the bitmap images. The transformation of the original bitmaps to square bitmaps of a smaller size (128×128) might have resulted in the loss of fine regions of osteophytes due to the reduction in resolution.

Another source of potential error comes from the alignment of the images. For the between femora dissimilarity measures, and the analyses resulting from them, to be meaningful there has to be a strong correspondence between pixel location and anatomical location that is consistent between all pairs of images. This consistency was enhanced by the translation of the images before the calculation of the dissimilarity measures. However, the consistency of the correspondence between pixel and anatomical location between pairs of femora is dependent upon the shape of the femora. There will be greater consistency for similarly shaped femora than for dissimilar femora.

The MDS results require a level of subjective interpretation. Although there are some guides as to what constitutes an adequate number of dimensions for representation of the data, there is no formal method for deciding how many ought to be used. In this study three dimensions

Table 3 Comparison of those femora within the lone intercondylar osteophyte subgroup with other osteophytic femora

Within subgroup?	Age group		Total (No)	Sex		Total (No)
	Younger No (%)	Older No (%)		Male No (%)	Female No (%)	
Yes	1 (4)	25 (96)	26	15 (58)	11 (42)	26
No	3 (6)	49 (94)	52	29 (37)	49 (63)	78
Total	4	74	78	44	60	104
p Value*		0.810			0.055	

*Resulting from Fisher's exact test.

were used: the benefit in STRESS reduction did not seem to outweigh the disadvantage of the complexity of displaying a configuration of points in four dimensions. There is also a degree of subjectivity in deciding what constitutes a subgroup from the MDS maps. We have, however, supported our interpretations with a cluster analysis, producing consistent results.

Owing to these issues, only obvious data structure has been discussed here rather than trying to identify less apparent and disputable subgroups of femora. Arguably, some genuine, finer data structure and subgroups might have gone undetected.

The collection of femora used for this study is not a random cross section of subjects. It has a high proportion of "older" subjects and late stage osteoarthritis is greatly overrepresented. None the less, this sample showed a great variety in the osteophyte location around the distal femur, indicating osteophyte formation to be heterogeneous.

The identification of a subgroup of subjects with lone intercondylar notch osteophytes, especially on the medial side, is entirely consistent with the findings of Kindynis *et al.*¹⁷ These investigators found intercondylar notch osteophytes present in nearly all femora used in their study and this led them to conclude that "Intercondylar osteophytes ... appear to be an early finding in degenerative disease." They further suggest that tunnel view radiographs would be useful for the diagnosis of early knee OA as this view will more readily identify intercondylar osteophytes than anteroposterior or lateral views.

The nature of the relation between intercondylar osteophytes and knee OA is, however, one of speculation. It has been suggested that osteophytes occur as a result of joint instability. If this is the case then the intercondylar osteophytes of the femur (and perhaps those of the tibia) are due to an instability that affects the area. The cruciate ligaments are intimately involved with the intercondylar region. They maintain a tight stability of the knee when the knee "screws home" at the end of leg extension and prevent the femur from slipping anteriorly in flexion and posteriorly in extension. A deficiency of, or damage to, these ligaments could cause an instability of the knee affecting this area. Wada *et al* speculate that intercondylar osteophytes are an attempt to restabilise an instability due to anterior cruciate ligament (ACL) dysfunction.¹⁸ They suggest that these osteophytes press against the degenerated or slackened ACL to increase stability. Eventually, however, in at least some cases, the decreased intercondylar notch width may itself cause cruciate ligament damage and further knee instability, leading to further osteophytosis and, perhaps, other features of OA.

However, the knee joint is complex, affecting the interfunctioning of several related structures. Joint instability, affecting the intercondylar area, could originate with a dysfunction of any other structures, such as the collateral ligaments or the menisci.

One possible scenario, therefore, is that these osteophytes are an indicator of knee instability,

which will inevitably lead to patent signs of OA, given sufficient longevity. Alternatively, one may reject the hypothesis that intercondylar osteophytes are related to knee OA: it has long been shown that osteophytes can occur within joints that do not develop any other structural changes typical of OA.^{14 15} These osteophytes may occur independently of other OA changes and be totally unrelated.

The "spiking" of the tibial tubercles of the intercondylar eminence of the tibial plateau has long been considered a feature of knee OA. For example, Reiff *et al* concluded that a lengthening and "sharpening" of the tubercles was related to the presence of OA.²⁶ This view has been challenged however. Although, Donnelly *et al* found a strong association between spiking and lengthening of the tubercles with the presence of lateral or medial osteophytes of the tibia,²⁷ they found no relation with joint space narrowing. Also, the relation of cartilage damage within the intercondylar notch region to cartilage damage elsewhere has been examined. A postmortem study of cartilage degeneration²⁸ found 16% of the 300 femora studied exhibited a linear area of cartilage degeneration on the inner aspect of the medial condyle which was considered unrelated to cartilage degeneration elsewhere.

The intercondylar region is one that has not been explored thoroughly. The area is difficult to investigate with anteroposterior radiographs, which have been commonly used to diagnose and investigate knee OA. Without further, clinical investigations, the nature of intercondylar osteophytes will remain speculative. The use of magnetic resonance imaging, rendering three dimensional images, should make the intercondylar notch region accessible for study in the future and allow comparisons to be made with soft tissues, including the cruciate ligaments. Also, previous studies have been cross sectional. A longitudinal, clinical study would be necessary to test the hypotheses outlined above relating to intercondylar osteophytes.

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Appendix

A simple count of the number of concordant or discordant osteophyte pixels between two images will treat any region of osteophytes not in common between two images the same. Rather, a dissimilarity measure which reflected the proximity of regions of non-common osteophytes was sought—that is, one which was greater between two images with regions of osteophytes further apart than between two images with the same amount of osteophytes closer together. Therefore, a dissimilarity measure was devised which was based upon steps of "expanded" regions of osteophytes. At each step, the regions of osteophytes on an image were expanded uniformly by a set number of pixels. Let the value of a pixel at location (i, j) after k stages of expansion be

denoted by P_{ijk} . Let this value be 0 if it is non-osteophytic and 1 if it is osteophytic. The value of any pixel after the next step of expansion—that is, after step $k+1$ is given by:

$$P_{ijk+1} = \max(P_{srk} : (i-s)^2 + (j-t)^2 \leq h^2)$$

where h is the distance of expansion (in pixels) at each step. In other words, any pixel at step $k+1$ which is within h pixels of an osteophytic pixel at step k then “becomes” an osteophytic pixel. Eight stages of expansion were used, each of 16 pixels (that is, $k=8$, $h=16$).

After each step of expansion a 2×2 contingency table could be constructed for any pair of images indicating the number of common or disparate expanded osteophyte pixels. A dissimilarity measure can then be based upon the resulting tables. A dissimilarity measure was defined based on the sum of these values over the eight steps of expansion.

For any image, the proportion of pixels exhibiting the feature of interest was relatively small. When comparing two images the number of matching negative-negative pixels is likely, in the first stages of expansion, to be large. Therefore, to avoid a dissimilarity measure being dominated by the large number of negative-negative pixel matches, it was decided to adopt Jaccard's measure,²⁹ which does not incorporate “negative-negative” matches.

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