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Research article

The potential for over diagnosis of Paget's disease of bone using macroscopic analysis

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ABSTRACT

Objective: This study explores the validity of Paget's disease of bone (PDB) reported in unpublished skeletal reports, based on macroscopic analysis alone.
Materials: The high prevalence of 'suspected' Paget's disease (10.7%) in an early modern sample from St John's the Evangelist Church in Redhill, Surrey is reassessed.
Methods: Signs of PDB were examined in 53 well-preserved adults aged 35 + years using macroscopic, radiographic and histological techniques.
Results: Macroscopic features of PDB were identified in 8 individuals (15%), with 5 individuals later rejected using radiography. Two individuals showed classic radiographic features of PDB, with a third presenting possible features in radiography (5.7%). These three cases were confirmed by histological analysis.
Conclusions: PDB should not be suggested as a single diagnosis in cases of bone hypertrophy without confirmation using radiography.
Significance: The growing popularity of 'big data' projects and limited collections access means that unpublished cases of PDB are often included in large scale analyses, impacting our understanding of the evolution of this disease. Using macroscopic analysis alone leads to overdiagnosis. Histological analysis is unnecessary when radiographic features are present, but provides a useful diagnostic step in long bones in advanced cases of PBD.
Limitations: The radiographic sample in this study was limited to three individuals.
Suggestions for further research: The conclusion that radiography alone can be used to identify PDB in archaeological cases merits further research on a larger number of cases.

1. Introduction

Paget's disease is a condition regularly identified in archaeological contexts. Clinical cases indicate that Paget's disease is most common among populations of British descent, with a prevalence of 1–3% in those older than 55 years (Ralston and Albagha, 2014; Cook and Wall, 2021). In a review of spine, pelvis and femur radiographs of 29,054 individuals over 55 years from 31 towns in Britain, Lancaster had the highest incidence of PDB in the 1980 s at 8.3%, although this had fallen to 3.7% by 1995 and 0.8% in 2017 (Barker et al., 1980; Abdulla et al., 2018). The high incidence of the disease in England, and in the north-west in particular, seems to be reflected in the archaeological record (Burrell et al., 2016; Shaw et al., 2019). In 2010, Mays reviewed cases of Paget's disease from the archaeological literature. Of the 109 published cases from northwest Europe, 94% (n = 103) were from England, peaking in the later medieval period. Where sex was reported, 71% of the cases were male, but the ages of the individuals affected was not provided. Mays (2010) used these data to argue for the British origins of PDB, but this theory is controversial and since 2010, 83 additional archaeological cases of PDB have been identified outside the UK, many sourced from non-English publications (Menéndez-Bueyes and Fernández, 2017; Rossetti et al., 2018; Kesterke and Judd, 2019; Spence et al., 2021). These data have been used to argue for a Mediterranean spread of the disease (Menéndez-Bueyes and Fernández, 2017). Further insight into the origin of Paget's disease came in 2019, when 4.6% of individuals from Norton Priory in northern England demonstrated a more severe form PDB, affecting 75% of the skeleton. Shaw et al. (2019) used ancient protein analysis to identify sequestosome 1 (SQSTM1) or p62, a protein centrally affected in Paget's disease, preserved in skeletal samples. Direct sequencing of the ancient DNA excluded contemporary

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Paget's disease associated SQSTM1 mutations as the cause of the Paget's identified at Norton Priory.

All of the above reviews are centred around published cases of PDB. Paget's disease is, however, frequently mentioned in reports that never reach publication. Such data is often consulted in both small scale and 'big data' projects, where skeletons are closed for access, reburied, or reassessment is not practical. An example of a big data study of PDB in the archaeological record is that by Pusch and Czarnetzki (2005), who examined over 8500 individuals from central Europe dating from (560 BP- 1500 CE), and suggested a disease prevalence rate of 0.03%, with no occurrence before AD 1400. These figures were ultimately contested by Waldron (2005) as being unreliable, as the study appeared to be based on macroscopic evaluation alone. Pusch and Czarnetzki (2005) also neglected to include older cases of the disease from Neolithic Europe (i.e. Pales, 1929; Arnautou et al., 2011).

To determine whether secondary data can be relied upon, we reassessed the prevalence of Paget's disease identified by macroscopic analysis in individuals from the early modern burial ground of St John's Church in Redhill, Surrey (1843–1904 CE). In the original assessment, 10 of the 93 adults (10.7%) in the sample were 'suspected' of having PDB. This included two 'adults' of unknown age and three individuals aged 35–44 years (Watts, 2016). To place this prevalence rate into context, a review of PDB in other post-medieval sites in southern England was carried out. One of the most popular sources of secondary data is the Wellcome Osteological Research Database (WORD database,) provided by the Centre for Human Bioarchaeology at the Museum in London. In our review of 1485 individuals in six post-medieval sites (Chelsea Old Church, Crossbones, St Brides Crypt, St Brides Lower Churchyard, Broadgate and St Benet Sherhog), the prevalence of PDB in London ranged from 0% to 4%, with an overall prevalence of 2.2% in 679 individuals older than 35 years. WORD does not indicate whether any of the cases were confirmed using radiographs. The real incidence of Paget's in the south of England during the nineteenth century is difficult to assess, as it was newly recognised, but Fairbank (1950) reported 50 cases per year in London radiography departments, suggesting it was not uncommon.

The reported cases of PDB at Redhill are high compared to other sites from south-east England at this time and may be the result of particular environmental circumstances at this site – or may indicate that the circumstances in which bioarchaeologists make an initial diagnosis of PDB needs to be strengthened to avoid inflated rates in our secondary data. Correct diagnosis of PDB is important if we are to understand the true evolution of the disease and its link to British ancestry.

1.1. Paget's disease of bone

Paget's disease is characterised by abnormal bone formation due to disruption in the normal equilibrium of osteoclasts removing bone, and osteoblasts forming new bone at the sites of bone resorption (Sabharwal et al., 2014). Adult cortical bone has a relatively low turnover rate of 2–3% per year, which maintains biomechanically strong bone (Clarke, 2008). The disturbance in bone remodelling observed in PDB is believed to be primarily caused by the action of abnormal osteoclasts (Tuck et al., 2017). They affect the rate of remodelling, which can increase up to 20 times more than normal (Mundy, 1999: 181). As longitudinal growth has ceased in adults, this disruption only affects intramembranous bone turnover, with joint surfaces remaining normal.

The pathogenesis of Paget's disease can be described in three phases: lytic, mixed, and sclerotic, although the clinical terminology used to describe these phases can vary (Brickley et al., 2020: 181). The first, or lytic phase, is characterised by an increase in osteoclastic activity causing bone resorption (Mirra et al., 1995). The second, mixed phase is marked by a combination of both osteolytic and osteoblastic activity, alongside marked bone formation. While the number of osteoblasts is greatly increased, it is suggested that their functional capacity remains normal (Kanis, 1991). The third and final phase is known as the sclerotic phase, where new disorganised fibrous bone is formed. This bone has a weakened architecture that predisposes it to fracture (Shaw et al., 2019). Paget's disease can affect one bone (monostotic) or several bones (polyostotic) with different phases of the disease able to coexist in the same bone at any one time (Winn et al., 2017). Whilst any bone can be affected, the axial skeleton is the most frequent site of Pagetic bone involvement, with common sites being the pelvis (67%), spine (39%), femur (33%), tibia (19%) and skull (25%) (Grauer and Roberts, 2019; Langston et al., 2007). It is common for multiple vertebrae to be affected, with normal vertebrae interspersed between them (Grauer and Roberts, 2019).

Second to osteoporosis, Paget's disease is the most common metabolic bone disorder in the UK (Tuck et al., 2017). Regardless of its frequency, its aetiology is not fully understood. Although a strong genetic association has been established, with several susceptible genes having been identified (Alonso et al., 2017), the focal nature of skeletal lesions, incomplete penetrance of the disease among family members, and overall reductions in the rates of the disease is suggestive of a genetic susceptibility triggered by one or more unknown environmental factors (Gennari et al., 2019; Abdulla et al., 2018; Lever, 2002; Audet et al., 2017). It is therefore important that Paget's disease in archaeological assemblages is recorded as accurately as possible to allow a deep time perspective of the evolution of this disease.

1.2. Macroscopic, Radiographic and Histological features

Unlike clinical cases, where raised serum alkaline phosphatase can identify Paget's disease, physical changes to the bone are looked for when assessing skeletal remains. Macroscopically, bone affected by Paget's disease has a more porous, pumice-like appearance, with denser cortical and trabecular bone that is harder, heavier, and larger than normal (Burrell et al., 2019; Grauer and Roberts, 2019; Whitehouse and Davies, 2006). Cranial bones increase in thickness. The shafts of long bones enlarge, thicken, and bow, especially in weight-bearing bones, due to their weakened architecture (Vallet and Ralston, 2016). This weakening of bone architecture also makes it prone to secondary fractures (Nepal et al., 2021). In his assessment of the multiperiod site of Barton-on-Humber, Lincolnshire, Waldron (2007:98) indicated that just over a third of the fifteen PDB cases were suspected on visual examination, with the rest only coming to light with the use of radiography. This highlights the difficulty of the identification of Paget's disease by macroscopic analysis alone.

Radiographically, osteoporosis circumscripta, a skull cap shaped area of resorption that usually crosses suture lines, is considered a unique feature of early Paget's disease (Mirra et al., 1995). Thickened cranial bones presenting with radio-dense areas that have a "cotton wool" appearance characterised by uneven zones of radiopaque and radiolucent bone, are a characteristic development in the second, mixed, phase (Cortis et al., 2011; Mirra et al., 1995). In the third phase, the skull is visibly enlarged with coarse sclerotic bone observable, particularly on the inner table (Brickley et al., 2020: 183). In long bones during the first stage, increased resorption can give bone a characteristic V-shaped (cutting cone) of radiolucency, which has been likened to a 'blade-of--grass', or 'flame shape' (Tuck et al., 2017; Rogers et al., 2002; Resnick, 2002). Pagetic vertebrae have a 'picture-frame' or 'ivory' appearance, caused by marginal bands of dense or radiopaque bone, which present as visible lines on a radiograph (Brickley et al., 2020; Roches et al., 2002; Resnick, 2005). Mirra et al. (1995), suggest four features identified through clinical radiographs that, if all are present, are pathognomonic of Paget's disease: V-shaped (cutting cone) of radiolucency, coarsening of trabecular pattern along stress lines, cortical thickening and enlarged bone contours (Table 1).

Histology can further indicate the presence of the disease. During the first lytic phase, hypervascularisation of the cortical bone is visible due to increased resorption. Howship's lacunae form at the site of bone removal (Brickley and Ives, 2020: 187; Mirra et al., 1995). In the

Table 1
Bone features of PDB identifiable through macroscopic, radiographic and histological methods.

Method	Bone feature
Macroscopic	Hypertrophy[1, 2, 3]
	Pumice-like bone[1, 2, 3]
	Cortical thickening[1, 2, 3]
	Long bone bowing[4]
	Secondary fracture[5]
Radiographic	Cranium, 'cotton wool' appearance[6, 7]
	*Osteoporosis circumscripta[7]
	Vertebrae, *ivory or 'picture frame' appearance[8, 9, 10]
	Long bones, *V-shaped (cutting cone) of radiolucency; coarsening of trabecular pattern along stress lines; cortical thickening;[7, 10, 11, 12]
Histological	Increase in Howship's lacunae forming at sites of bone removal[7, 13]
	* 'Mosaic pattern' to the cementum lines of lamellar bone[9]

*single features identified as pathognomonic of the disease
[1] Burrell et al. (2019); [2] Grauer and Roberts (2019); [3] Whitehouse and Davies (2006); [4] Nepal et al. (2021): [5] Vallet and Ralston (2016); [6] Cortis et al. (2011); [7] Mirra et al. (1995); [8] Brickley et al. (2020); [9] Roches et al. (2002); [10] Resnick (2005); [11] Tuck et al. (2017); [12] Rogers et al. (2002); [13] Brickley and Ives, 2020.

trabecular bone, there is an increase in osteoclastic resorption and focal thinning. The second, mixed phase sees the start of the characteristic pattern of irregular cement lines joining areas of lamellar bone, often referred to as having a 'mosaic' appearance (Roches et al., 2002; Brickley et al., 2020: 187). From the late second phase to the final phase, the bone cortex has decreased vascularity with sclerotic bone (Brickley and Ives, 2020: 187).

2. Materials and methods

2.1. The study sample

Redhill, Surrey is a town located south east of London, England (Fig. 1). The construction of the London to Brighton railway line in 1841 led to the expansion of the Redhill area (formally known as Warwick Town). The development of this rail network resulted in an increase in the labouring population and the construction of St. John's the Evangelist Church in 1843 (Moore, 1999). The main burial period for St. John's Church was between 1843 and 1896; however, due to family plots, a reduced number of burials took place up until 1968 (Kefford, 2015). Burial registers from 1843 to 1905 list the name, date of burial and age at death of 3626 individuals interred in the cemetery grounds (Church of England Burial Record, 1843–, 1905).

In 2015–6, 5% of the cemetery of St John's Church was excavated. A total of 296 individuals were exhumed, and 250 individuals who predated 1905 underwent preliminary analysis (157 non-adults; 93 adults). These individuals are currently cared for by the Department of Archaeology, University of Reading awaiting reburial.

2.2. Methods

A total of 92 adults were reanalysed, with 53 selected for detailed analysis to determine the presence of Paget's disease, as they were aged over 35 years and were 25% complete. These individuals were selected as the disease is more likely to be identified in well-preserved individuals and Paget's disease normally affects adults from mid to old age.

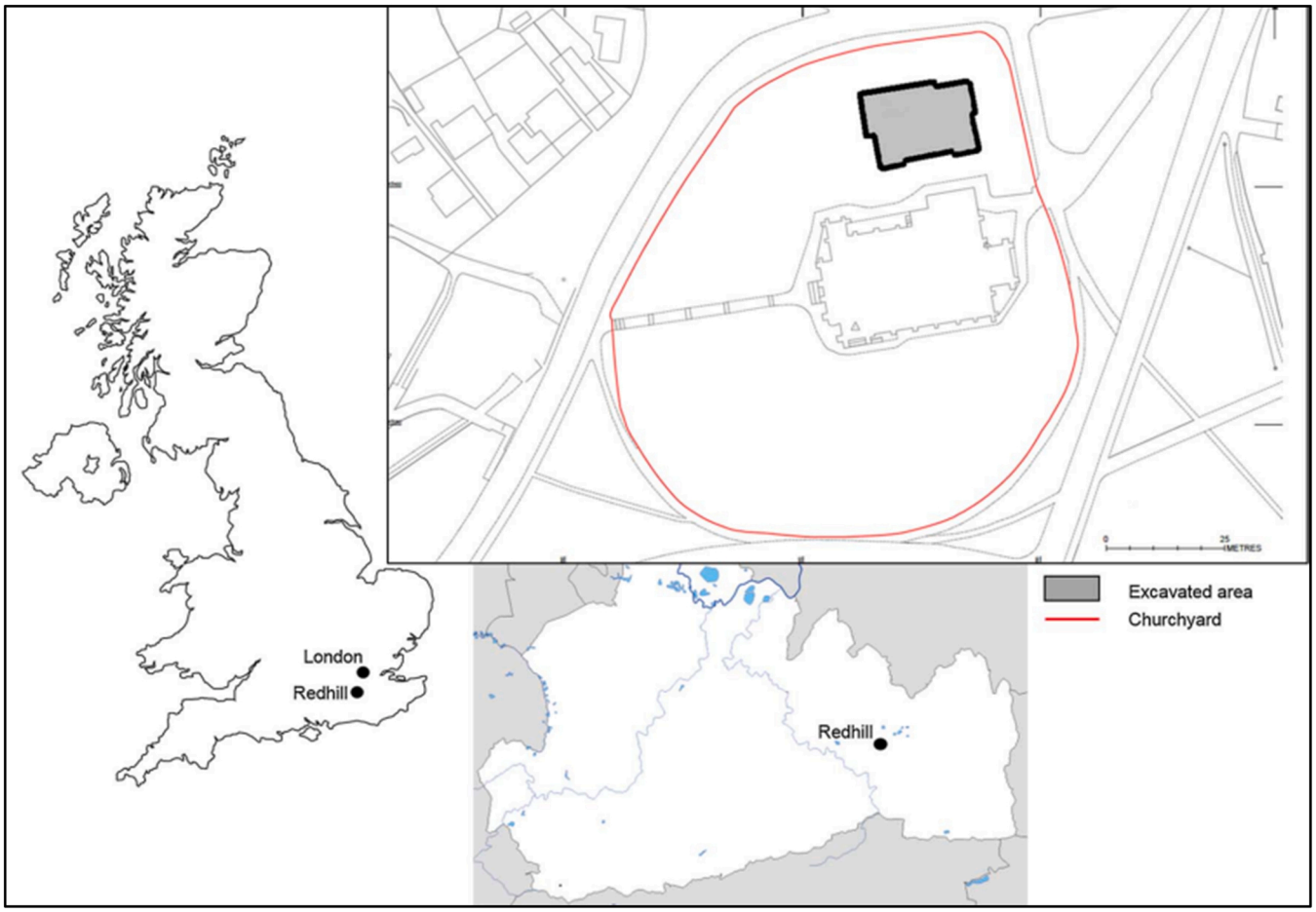

Fig. 1. Location of St. John's Church, Redhill, Surrey, UK (from Watts and Valme, 2018: 63).

During macroscopic analysis, any bones that appeared enlarged, heavy, pumice-like or thickened were recorded (Burrell et al., 2019; Whitehouse and Davies, 2006). Weight-bearing long bones were examined for signs of bowing and any fractures were recorded, as both are recognised as secondary effects of the disease due to weakened bone architecture (Grauer and Roberts, 2019). Rogers et al. (2002) identified a case of PDB in the archaeological record following the radiography of a fracture. Individuals with evidence for neoplastic transformation were also identified since neoplasia is a complication of the disease, albeit rare (Altman, 2003). Individuals with features associated with Paget's disease were selected for radiographic analysis.

Medio-lateral and antero-posterior radiographs were taken using a Hewlett-Packard Faxitron Series Cabinet X-Ray System and viewed using a CareStream Vita Flex CR X-Ray Scanner and Image Suite. When possible, the affected and non-affected sides were radiographed together to enable comparison. The kilo Volt (kV) was adjusted depending on bone thickness (45 or 55 kV) with an exposure between 3 and 4 s. The radiographs were then analysed for classic features of PDB. Individuals with features consistent with PDB were then selected for histological analysis, as was a control sample.

To prepare the thin sections, samples of around 1 cm by 1 cm were taken from areas with evidence of pathology using a Dremel Lite

Table 2
Paget-like changes visible macroscopically, radiographically and histologically. Orange indicates specific bones selected for histology. Green highlights cases of possible Paget's disease.

Skeleton	Sex and age	Bone with macroscopic Paget-like changes	Paget-like changes in radiograph?	Paget like changes in histology?
1466	Female 45+ years	Occipital bone	No	NA
		Frontal bone	No	
		Right femur	No	
		Lumbar vertebrae	No	
1645	Female 45+ years	Left ulna	Possible	Yes
1691	Male 45+ years	Occipital bone	Yes	Yes
1733	?Male 45+ years	Cranium	Yes	Yes
		Maxilla	Yes	NA
		Right femur	Yes	Yes
		Left Ilium	Yes	NA
		Vertebrae T11-L1	Possible L1	Yes
1762	Male 45+ years	Cranium	Slight thickening	NA
		Mandible	Slight thickening	
1874	Female 45+ years	Cranium	Slight thickening	No
1931	Female 45+ years	Cranial fragments	No	NA
1985	?Female 45+ years	Cranium	Slight thickening	NA
		Mandible	No	

cordless precision drill, in a manner to cause the least visible destruction as possible. Former trays were created for each sample from 125 μm thick aluminium foil. Four-part epoxy transmit resin was added to each sample former and the samples were then vacuum embedded in a vacuum chamber, removing as much air as possible from the samples. They were then cured for 18 h at 30° centigrade. The foil tray was removed and the surface polished on a rotary polisher with increasingly fine grit paper to reveal the cross section of the bone. They were then left to dry, after which the cross-section surface was cleaned with petroleum ether and cleaned with lint free wipes. RT152 epoxy resin was used to mount the smooth and cleaned cross sectioned surface to a glass slide. The affixed samples were then cut down to 0.5 mm thickness with an Abrasi Met 250 cutter. They were then hand polished with increasingly fine diapad hand lap polishing pads to around 100 μm. The samples were viewed through a Leica DM EP microscope, with images captured through LAS camera software. Features of PDB were then looked for in the captured images.

3. Results

In the initial reassessment of 92 individuals from Redhill, two individuals previously identified as having Paget-like hypertrophy were disregarded as the changes fell within the range of normal variation. Conversely, two individuals not originally highlighted in the report were considered to have hypertrophy consistent with Paget-like changes (SK 1645 and 1691). In the reduced sample of 53 individuals, 19 or 36% presented with at least one fracture. While they had no outward signs of PDB, they were selected for radiography, as there have been reports of cases identified in the archaeological record after routine radiographs of fractured bones (Rogers et al., 2002). No radiographic signs of Paget's were detected in these individuals. This included two individuals (SK 1874 and 2173) whose fractures were accompanied by bone hypertrophy that could have signalled the presence of PDB.

Of the 53 individuals subjected to detailed analysis, 8 (15%) individuals had macroscopic changes consistent with a possible presence of PDB (3 males; 5 females). All were over the age of 45 years (Table 2). When radiographed, only 2 of these 8 individuals had radiographic features associated with the disease (SK1691 and SK1733), with a third individual (SK1645) presenting with possible radiographic features (Figs. 2–4). Those discounted at this stage included three individuals (SK 1762, 1874 and 1985) with cranial thickening suggestive of PDB during macroscopic analysis. A thin section was taken from SK1874, which confirmed this negative diagnosis (Fig. 5). Histological analysis of the two individuals showing radiographic changes associated with PDB (SK1691 and SK1733) confirmed a diagnosis of the disease (Figs. 3 and 4). In the case of SK1645, a thickened cortex, coarse trabeculae and the patchy appearance of the cortex (similar to the 'cotton wool' sign) were highly suggestive of Paget's disease but sclerosis would have eliminated a distinctive V-shape feature in an advanced case. In this example, histology was necessary to confirm a diagnosis through the presence of 'mosaic' Haversian systems (Fig. 2). The overall prevalence of Paget's disease at Redhill was 5.7%, or three of the 53 individuals.

4. Discussion

The reassessment of the Redhill sample excluded two individuals

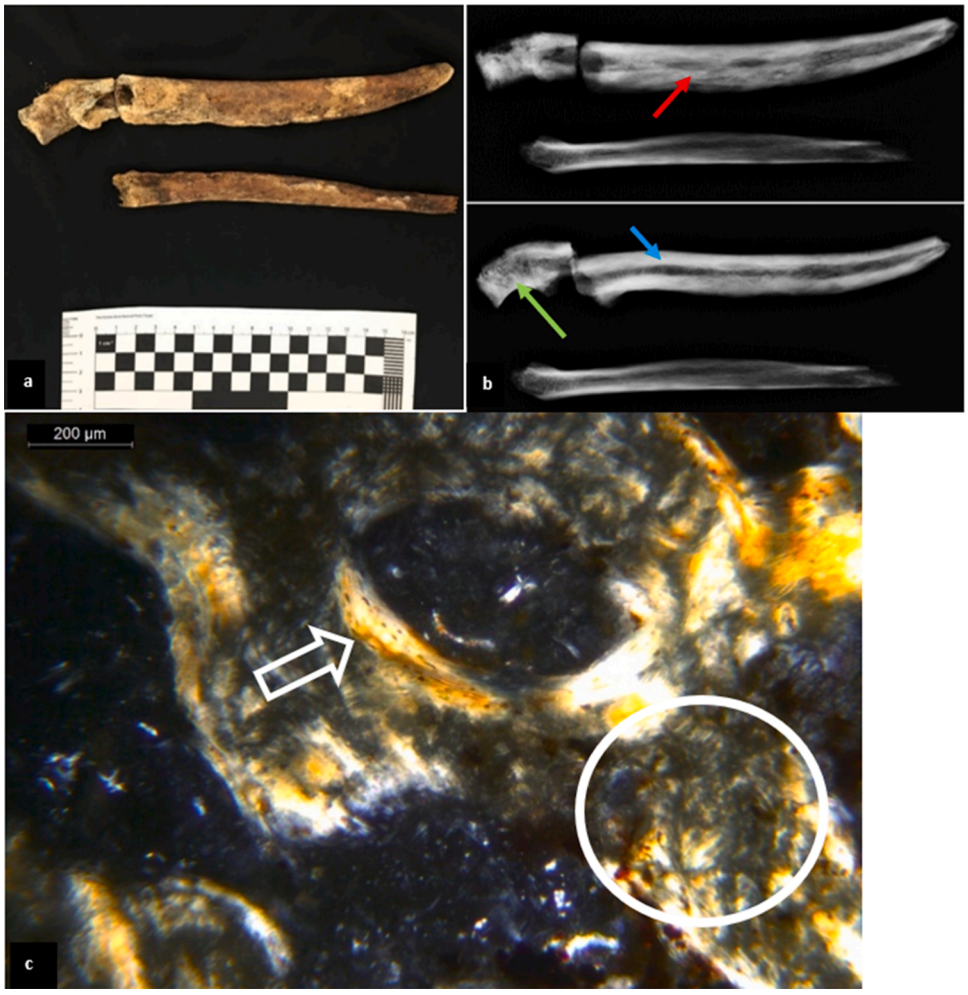

Fig. 2. SK1645, left ulna. **a)** Macroscopic appearance showing hypertrophy of the left ulna (top), compared to the shaft of the right ulna in the same individual (bottom). **b)** Radiograph: Taken from an antero-posterior view (top) and a medio-lateral view (bottom), with the right ulna for comparison. The red arrow shows an area of sclerotic bone. The blue arrow shows cortical thickening and enlarged bone contours. The green arrow highlights an area of coarsening of trabeculae. **c)** Histology: Transverse section of the ulna in white light (200 μm scale shown). Showing un-organised 'mosaic pattern' of Paget's disease (white circle). The white arrow indicates an area of normal lamellar bone adjacent to the mosaic feature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

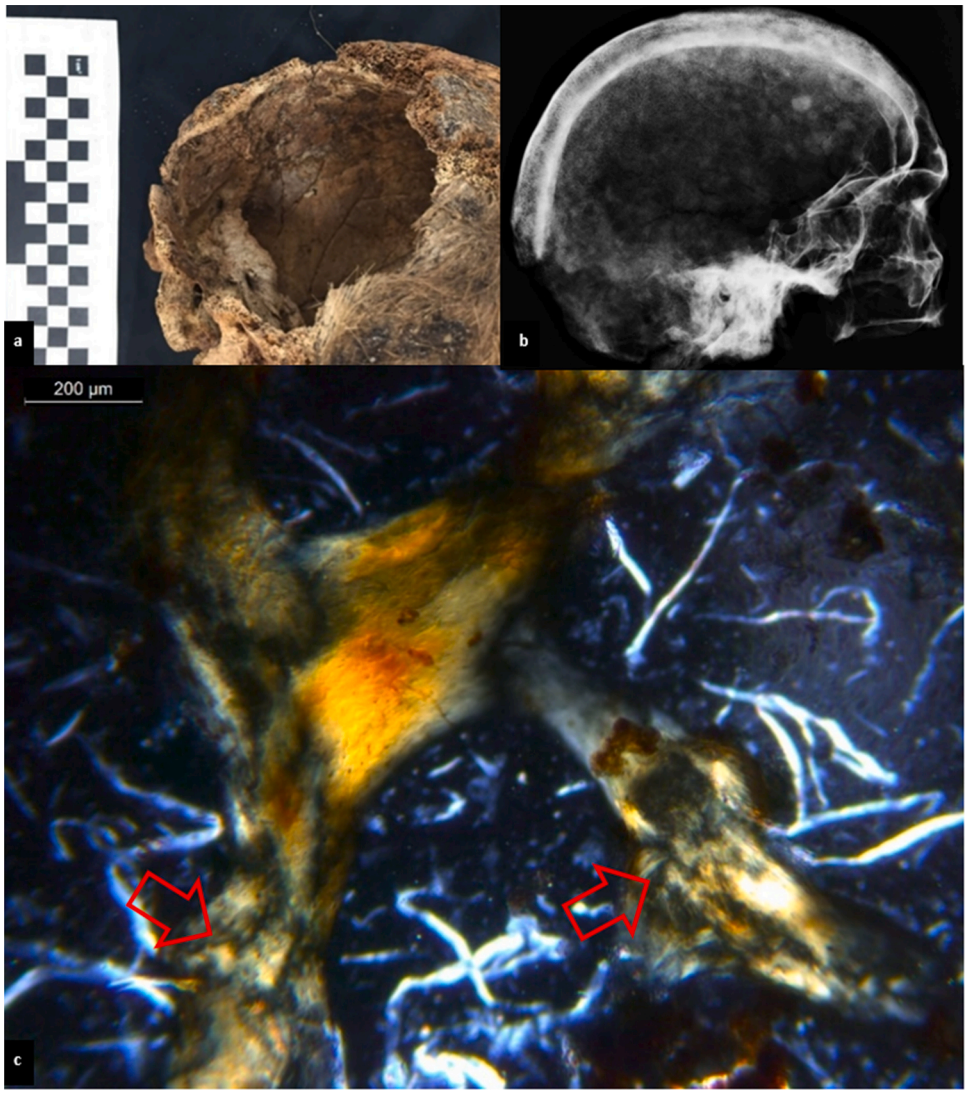

Fig. 3. SK1691, cranium. **a)** Macroscopic appearance showing a thickened occipital bone. **b)** Radiograph: From a medio-lateral view. The cranium shows a 'cotton wool' appearance, cortical thickening and enlarged bone contours consistent with Paget's disease. **c)** Histology: Transverse section of the occipital bone in white light (200 µm scale shown) demonstrating a disorganised lamellar bone arrangement (red arrows) with no clear structure to the Haversian system. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suggested to have PDB in the original report, as they did not have any macroscopic lesions indicative of the disease. It also identified two individuals who were not mentioned in the initial assessment that went on to be cases confirmed by radiographic and histological analysis as having changes consistent with PDB. The prevalence of Paget's disease in the Redhill sample was reduced by almost half from 10.7% (Watts, 2016) to 5.7%. The study sample included 20 individuals aged between 35 and 44 years to reflect the original study and to capture any evidence for early onset PDB, identified in medieval individuals with an ancient strain of the disease (Shaw et al., 2019; Burrell et al., 2016). Only individuals over the age of 45 years were identified with Paget's in the Redhill sample, raising the prevalence rate in this age cohort to 9% (n = 3/33). This is high in comparison to post-medieval London sites (0–2.9%) and modern rates of 1–3%, but similar to Lancaster rates in the 1980 s (8.3%), but much less than the 18.8% that would have been reported for Redhill if the preliminary results had been adjusted for age.

These results illustrate issues with the diagnosis of PDB by macroscopic analysis alone, and the potential for over diagnosis of the disease in the past using unpublished secondary data. The problematic diagnosis of PDB from macroscopic appearance is well known. Mays' (2010) review of cases confirmed by radiography and/or histology, reduced the sample of European cases from 109 to just 37. These problems with the diagnosis of Paget's disease highlight the need for rigor in its identification, and an awareness that further methods of analysis, such as radiography, are required to draw conclusions (Buikstra et al., 2017). Central to palaeopathological practice are accurate descriptions and a thorough differential diagnoses to improve our decision-making processes and make them more transparent (Klaus, 2017). Even stating 'possible' or 'probable' Paget's disease in instances when remains cannot be re-examined and no images are provided, reduces attempts at definitive diagnosis (Zuckerman et al., 2014). The differences in the number of cases of Paget's disease between the original report and the reassessment are understandable, as initial skeletal assessments are often undertaken under time restraints and with limited available resources, diagnoses are often reliant on visual observation. Macroscopic analysis acts as the first indication that a bone complies with expected patterns of a disease, while radiography represents an analytical process for diagnosis (Mays, 2020). This highlights the importance of revisiting previously identified cases of Paget's disease and allowing a period of retention and study before reburial.

The correct identification of Paget's disease in skeletal remains adds to our understanding of modern clinical cases. In fact, when osteitis deformans was first described by James Paget in 1887, clinicians believed it was a new disease until early palaeopathologists identified cases dating back to the Neolithic (Pales, 1929; Arnautou et al., 2011), although some of these diagnoses should be treated with caution (e.g. Denninger, 1933 see Cook, 1980). Analysis of ancient proteins has identified an ancient form of the disease that is no longer present today

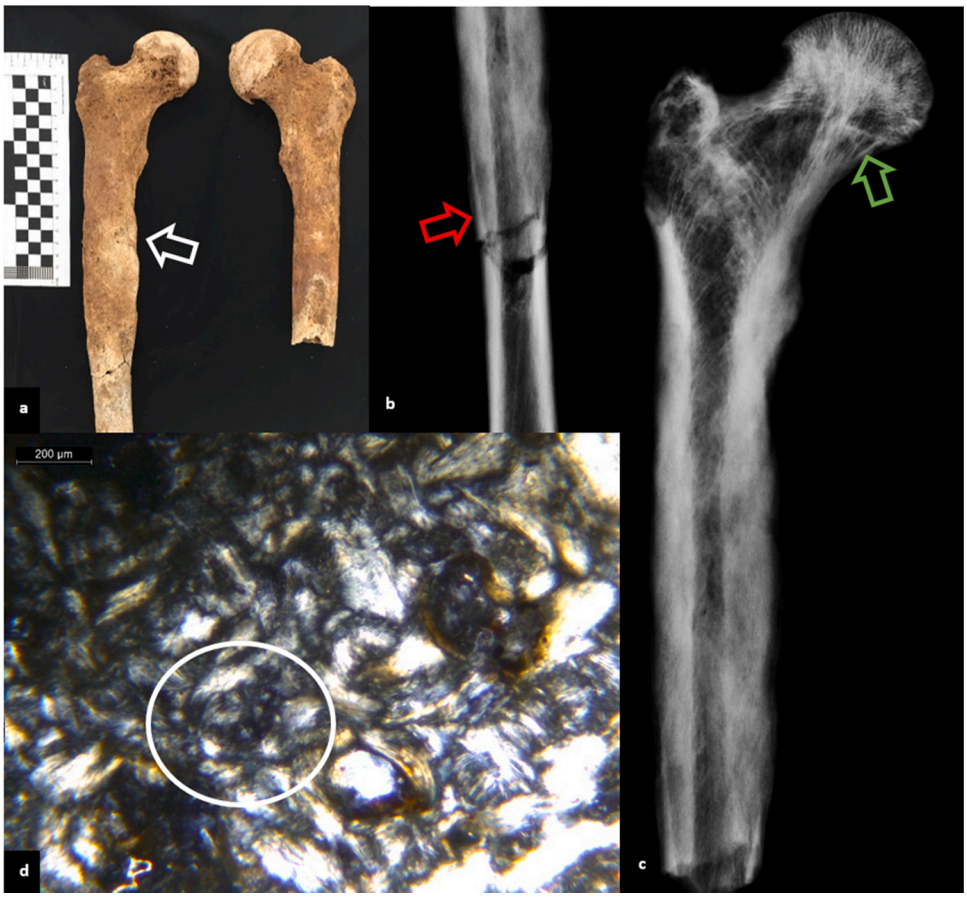

Fig. 4. SK1733, right femur. **a)** Macroscopic appearance showing hypertrophy of the bone dimensions compared to the left femur from the same individual (right). Cortical thickening and contour change is evident throughout the shaft, particularly visible at the white arrow. **b)** Radiograph: From an antero-posterior view. The red arrow indicates a dart of radiolucency visible under a postmortem break of the shaft. **c)** The green arrow indicates an area of thickened trabeculae. **d)** Histology: Transverse section of the femoral shaft in white light (200 µm) showing some unorganised lamellar bone with a 'mosaic-like' appearance, particularly evident within the white circle. The cranium and first lumbar vertebra (not shown) also presented with hypertrophy, a 'cotton-wool' appearance on radiograph (cranium), and a similar disorganised Haversian structure (see Fig. 5c for comparison). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Shaw et al., 2019). These studies inform modern clinical understandings of the disease and potentially provide a clearer picture of its aetiology. However, prevalence rates over time can only be understood if cases are recorded consistently and accurately.

The preliminary Redhill report over diagnosed cases of 'suggested' Paget's disease by 5% when assessing macroscopic changes alone. This contrasts with the post-medieval prevalence rates in London downloaded from the WORD database, where cases identified through macroscopic analysis were much lower than those in modern populations. This more common trend has led many palaeopathologists to argue that macroscopic analysis alone will under diagnose the disease (Rogers et al., 2002; Waldron, 2005, 2007; Pusch and Czarnetzki, 2005). Luckily, Redhill has been retained for more detailed analysis. What is clear is that reporting cases of Paget's disease based on macroscopic analysis alone is not reliable or advisable. Qualifying adjectives such as 'probable', 'possible' or 'suggested' Paget's disease may be ignored in large-scale analyses, yielding a skewed assessment of the rates of the disease through time. It is recommended that the term bone 'hypertrophy' (alongside differential diagnosis) should be included in human bone reports and datasets, instead of 'possible' or 'probable' Paget's disease, unless or until radiographic confirmation is available. In addition, this study suggests that at Redhill, at least, cases of PDB could not be identified by targeting those with bone fractures, or that people with fractures represent a hidden cohort of Paget's disease sufferers.

In 1980, Cook re-examined an ancient case of Paget's disease originally published by Denninger (1933). The case was rejected using histology, but as no radiographs were taken, it is not possible to determine whether the case would have been rejected based on radiography alone. Ours is the first study to directly compare the evidence for Paget's using macroscopy, radiography and histology. De Boer and Van Der Merwe (2016) argue that although in many cases the diagnostic hallmarks of Paget's disease are lost in dry bone histological sections, the "mosaic" appearance of the later stages of Paget's disease is valuable for a definitive diagnosis. The current study argues that radiography can sufficiently confirm or reject a diagnosis of Paget's disease quickly and without the need for further destructive analysis to make a 'definitive' diagnosis.

There is one example in archaeology where a bone, a fibula, had a normal macroscopic and radiographic appearance, but demonstrated the typical microscopic "mosaic" appearance of advanced Paget's disease (Mays and Turner-Walker, 1999). In this case, many other bones in the skeleton of this individual presented macroscopic changes that could be confirmed radiographically as being Pagetic without the need for thin sections. In the current study, radiography alone was not sufficient to confirm PDB in a mature female with only one surviving bone showing hypertrophy. The advanced nature of the disease meant that any potential 'V-shaped' radiolucent feature would have been obliterated, and the other features could have been the result of other causes (e.g. neoplasia, infection). In this case, histological analysis was required. Hence, while radiographic analysis is sufficient in the majority of cases, thin sections are necessary to identify advanced (sclerotic) stages of the disease when radiographic features of all the affected bones are inconclusive.

Although this particular study is based on a limited sample, it merits future research. Recently, micro-CT scans have been used in the identification of Paget's disease (Kesterke and Judd, 2019; Wade et al., 2009). This method of analysis is promising, as it allows for a cross section of bone to be viewed without destruction. However, this method is currently expensive, requiring access to highly specialist equipment, unlike radiography. Brickley et al. (2020), have shown that even the early stages of PDB are visible radiographically through the identification of focal radiolucency, or a V-shaped (cutting cone) of radiolucency.

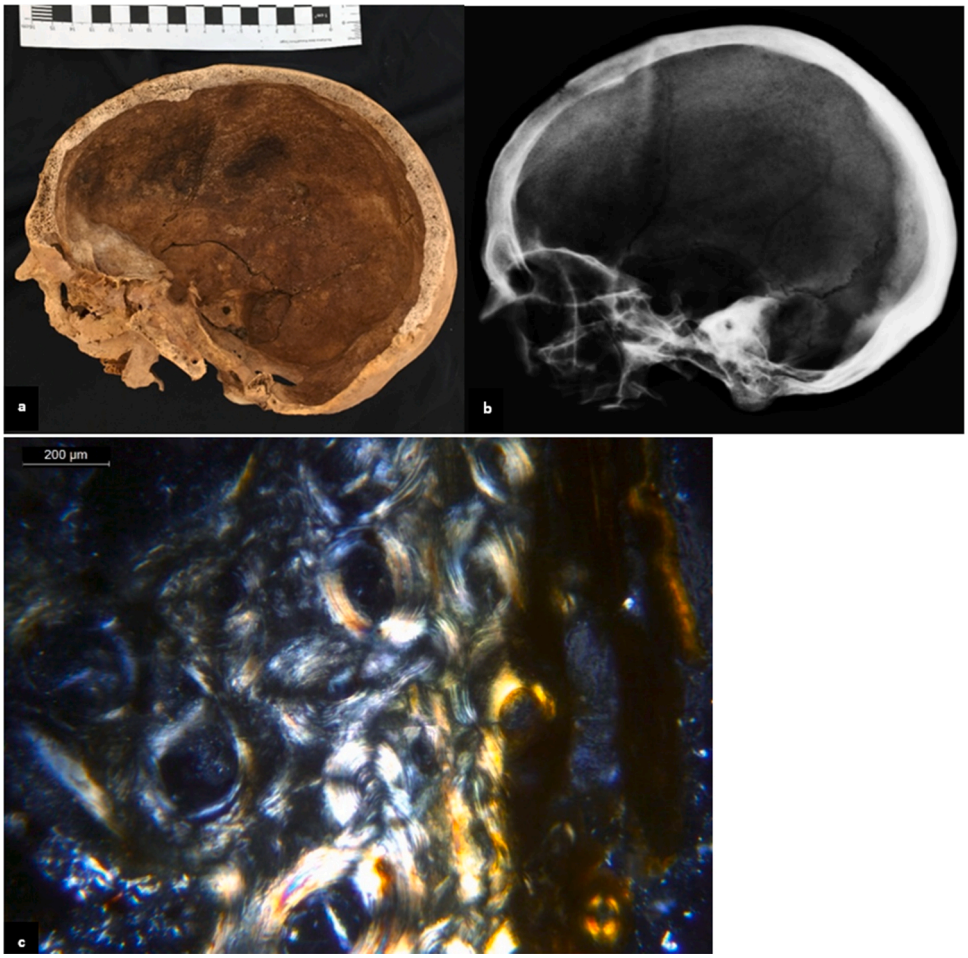

Fig. 5. SK1874, cranium. **a)** Macroscopic appearance showing hypertrophy of the skull (medio-lateral view); **b)** Radiograph: From a medio-lateral view. The cortex is dense and radio-opaque suggestive of a thickened cranium, but there is no evidence of a patchy 'cotton wool' appearance; **c)** Histology: transverse section of the frontal bone in white light (200 µm scale shown). Showing normally formed osteons within a clear Haversian system in comparison to Fig. 4c.

Histology at this point would present an increase in Howship's lacunae, with the typical "mosaic" appearance not evident until the disease was more advanced and macroscopic features had begun to appear. Diagnostic histological features are therefore not visible any earlier than radiographic ones.

5. Conclusion

This research has emphasised the need for caution when identifying Paget's disease in published and unpublished skeletal reports and datasets, especially when they are based on macroscopic changes alone. At Redhill, the original prevalence of 10.7% included individuals who showed no obvious signs of hypertrophy, and individuals who had thickened skulls with no radiographic or histological indication of the disease. The retention of this collection allowed for a reanalysis that identified two individuals with the radiographic and histological signatures of Paget's disease who were previously unrecorded. Based on this study we make several recommendations:

1. That any bones exhibiting hypertrophy or a pumice-like appearance based on macroscopic analysis alone be described as such, rather than being referred to as 'possible' or 'probable' Paget's disease
2. That differential diagnosis be included in the discussion of these bones to highlight the unspecific nature of these changes
3. That a diagnosis of Paget's disease could be made on the basis of radiography when characteristic signatures are identified
4. Histology is only required in advanced cases where none of the surviving bones show conclusive radiographic features
5. That wherever possible, collections are retained for a period of time to allow for further in-depth analysis.

In a world where the information collected from skeletal assemblages is being entered into open access databases, a need for consistent terminology is required. Over diagnosis prior to further research can be as much of a problem for our understanding of the past as under diagnosis. The recording and subsequent reburial of assemblages before further analysis can take place can result in erroneous datasets and these errors may be perpetuated if data are used without caution. These factors are especially relevant in relation to Paget's disease, where future study could aid in creating a comprehensive understanding of the aetiology of this debilitating disease and contribute to modern clinical knowledge.

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