The association between skeletal lesions and tuberculosis diagnosis using a probabilistic approach

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ABBREVIATED TITLE

TB-related skeletal lesions

KEY WORDS

differential diagnosis; paleoepidemiology; tuberculosis; specificity; sensitivity

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Abstract
Sensitivity and specificity estimates for 18 skeletal lesions were generated from modern skeletal samples for future paleoepidemiological analyses of tuberculosis (TB) prevalence in archaeological samples. A case-control study was conducted using 480 skeletons from two 20th century American skeletal collections. One-half of the skeletons were documented TB cases (Terry Collection), and the remaining age and sex-matched skeletons were controls (Bass Collection). The association between 18 candidate skeletal lesions and TB was established by comparing lesion distributions in case and control groups. Skeletal lesion indicators at six locations – the visceral surface of ribs, ventral part of thoracic and lumbar vertebral bodies, lateral part of ilium, acetabular fossa, iliac auricular surface, and ulna olecranon process - occurred significantly more often among cases than in controls, and were associated with one another. The most useful TB indicator proved to be a bony reaction on ventral thoracic and lumbar vertebral bodies. Its presence means a 53.3% probability of a true TB diagnosis. Because of the nature of the reference sample – 20th century American cases – the sensitivity and specificity estimates will better estimate disease prevalence in archaeological samples from cultural settings where pulmonary TB predominated. The general approach of this proof-of-concept study is applicable to other diseases that occur commonly and affect bone.

1. Introduction

Tuberculosis (TB), a mycobacterial disease, has deep roots in prehistory, and it remains a major public health concern throughout much of the world today (Bates and Stead, 1993; Daniel, 2006, 2009; Davies et al., 1999; Dheda et al., 2016; Grange et al., 2001; Grange and Zumla, 2002; Maher and Raviglione, 2005; Stone et al., 2009). It is of particular interest to paleopathologists because TB affects bone, so it is detectable in archaeological skeletons. That allows the disease to be identified where medical or historical sources are absent, scarce, or otherwise uninformative (Arriaza et al., 1995; Mays et al., 2001; Nicklisch et al., 2012; Ortner, 2003; Roberts and Buikstra, 2003; Steinbock, 1976). Typically, that is done through matching pathological lesions in archaeological skeletons to those found in recent documented cases, notably those from preantibiotic contexts (Buikstra, 1976; Ortner, 2008, 2012; Santos and Roberts, 2006). Archaeological remains have also yielded ancient DNA (aDNA) and mycolic acid profiles associated with mycobacteria that cause TB, complementing examinations of skeletal remains (Arriaza et al., 1995; Donoghue et al., 2004, 2017; Gernaey et al., 2001; Hershkovitz et al., 2008; Lee et al., 2015; Mays et al., 2001; Nicklisch et al., 2012; Pósa et al., 2012; Taylor et al., 2007).

Despite the importance of establishing where and when a disease such as TB was present, documenting its existence does not tell us whether the disease was common or not, hence its impact on past communities. Estimating disease prevalence in archaeological samples, let alone establishing what happened in once-living populations, requires a different approach involving a wide array of skeletal lesions, not just the most distinctive ones, each with an estimated sensitivity and specificity (Boldsen, 2001, 2005a, 2005b, 2008; Boldsen and Mollerup, 2006; Boldsen et al., 2013; Milner and Boldsen, 2017). Sensitivity is the probability of having a particular skeletal lesion given that the individual actually had the disease. Specificity is the probability of not having the skeletal lesion in people who did not have the disease. Such estimates, which accommodate the diagnostic efficacy of different skeletal lesions, are an important component of paleoepidemiological studies (Boldsen 2005a; Milner and Boldsen 2017).

Sensitivity and specificity estimates for TB are generated here for use with archaeological collections. They shift a researcher's attention from the identification of diseases experienced by specific individuals – a process particularly susceptible to misdiagnosis when only bones are available (Miller et al., 1996) – to a quantifiable probabilistic assessment of disease prevalence in a skeletal sample. Putting a sample-oriented approach into effect requires a set of lesions associated with the disease in question. Such information is available from clinical cases of TB (Aufderheide and Rodriguez-Martin, 1998; Martini, 1988; Ortner, 2003; Steinbock, 1976; Tuli, 2010) and modern reference collections where the disease is listed in individual medical histories, often as the cause of death (Kelley and El-Najjar, 1980; Kelley and Micozzi, 1984; Mariotti et al., 2015; Matos and Santos, 2006; Roberts et al., 1994; Santos and Roberts, 2001, 2006; Steyn et al., 2013). Building on that work, and through examining 480 American skeletons from the Robert J. Terry Collection (cases) and William M. Bass Donated Collection (controls), this case-control study estimates the sensitivity and specificity of 18 bony lesions plausibly linked to TB. These figures, in turn, can be used in paleoepidemiological studies to estimate the prevalence of TB in prehistoric and historic-period skeletal samples where pulmonary TB is thought to be the dominant form of infection attributable to the *Mycobacterium tuberculosis* complex.

2. Material and methods

2.1. Skeletal Sample

One-half of the 480 skeletons examined in this study are from the Robert J. Terry Collection at the Smithsonian Institution. These 240 skeletons have TB listed as the primary cause of death on death certificates. This skeletal collection, originally from St. Louis, Missouri, consists of people who for the most part died during the 1920s to 1950s (Hunt and Albanese, 2005). They tend to be of low

socioeconomic status, and information on sex, age, year of birth and death, ancestry, and cause of death are available for most of them. The collection is chosen because many individuals – more than 15% – are said to have died from TB. Because most of the deaths occurred in the pre-antibiotic era, the form of lesions and their distribution are likely to be as close to what might be found in archaeological samples as might reasonably be found in a modern documented skeletal collection.

Despite being a good collection for TB cases, the Terry Collection is not suitable as a source of controls. That is because TB was widespread in early twentieth-century America, especially among people who lived in poor conditions, which could be truly deplorable at that time in the St. Louis area. Although TB was in decline a century ago, in large American cities it was still the leading infectious disease cause of death in 1900, and it only lagged behind pneumonia in 1936 (Cutler and Miller, 2005). Therefore, no mention of TB in the records that survive for a particular individual cannot be regarded as evidence that the disease and, perhaps, its associated skeletal lesions are truly absent.

The other half of the sample, 240 skeletons from the William M. Bass Donated Collection at the University of Tennessee, are treated as controls. These individuals, many of whom resided in the Midsouth, died from the 1980s to the present day (Jantz and Jantz, 2008; Shirley et al, 2011). There is no indication of TB, or any other pulmonary condition, in the records for the skeletons examined. Although it is unlikely that people included in the study developed TB, the oldest ones might have been exposed to the pathogen when they were young, but never had outright symptoms of the disease. With regard to TB, the United States in the recent past has been considered a low-burden country, and both case and mortality rates have been declining throughout the late twentieth century (CDC, 2008; Hermans et al., 2015; Jung et al., 2010; McCray et al., 1997; Murray, 1989). Overall TB prevalence has been low; for example, in 2007 there were 2.1 TB cases among 100,000 people who were born in the United States (CDC, 2008). Prevalence varies among ethnic groups, being lowest among whites that make up 92% of our controls. That means an unrecognized TB case – one where the records are silent for TB – is unlikely to be included among the 240 skeletons examined.

The age and sex composition of the TB and control samples are not exactly the same. Nevertheless, as far as possible the Bass controls are matched in terms of sex and age to the Terry TB cases (Table 1).

Table 1. Distribution of 480 individuals by sex, age, and TB status in the Terry and Bass collection samples.

		N	%	Terry		Bass	
				N	%	N	%
Sex	Female	142	29.6	65	27.1	77	32.1
	Male	338	70.4	175	72.9	163	67.9
Age group (years)	15-25	52	10.8	37	15.4	15	6.3
	26-40	159	33.1	98	40.8	61	25.4
	41-60	193	40.2	77	32.1	116	48.3
	61-80	76	15.8	28	11.7	48	20.0
Assumed TB status	Positive	240	50.0	240	100.0	0	0.0
	Negative	240	50.0	0	0.0	240	100.0

2.2. Skeletal Lesions

Potential TB indicators were identified on the basis of clinical studies of radiological images and autopsies (Davidson and Horowitz, 1970; Martini, 1988; Sorrel and Sorrel-Dejerine, 1932; Thijn and Steensma, 1990; Tuli, 1975, 2010); modern skeletal reference samples (Kelley and El-Najjar, 1980;

Kelley and Micozzi, 1984; Matos and Santos, 2006; Roberts et al., 1994; Santos, 2000; Santos and Roberts, 2001, 2006; Steyn et al., 2013); archaeological skeletons, sometimes complemented by aDNA and mycolic acid analyses (Baker, 1999; Baker et al., 2015; Buikstra, 1976; Donoghue et al., 2017; Gernaey et al., 2001; Hajdu et al., 2012; Lee et al., 2015; Mays et al., 2001; Milner and Smith, 1990; Nicklisch et al., 2012; Pálfi et al., 2015; Roberts and Buikstra, 2003; Zink et al., 2005); paleopathology reference works (Aufderheide and Rodriguez-Martin, 1998; Ortner, 2003; Steinbock, 1976; Zimmerman and Kelley, 1982); and the research team's experience examining modern and archaeological specimens from different time periods, cultural settings, and continents. Eighteen indicators were initially scored for TB-related skeletal changes. All of them, except those on ribs and vertebrae, were recorded for the left and right sides of the skeleton.

Potential TB indicators were scored as absent (0) or present (1). Cutoff points for scoring a lesion as present were intentionally set low. That means mild stages of the disease's progression are likely to be recorded, although doing so increases the possibility that a positively scored trait was unrelated to TB.

2.3. Statistical procedure

Data management and analyses were carried out with STATA 13 for Windows. In analyses of candidate indicators and their relationship to TB, the left side of bilateral traits was usually used. If the left bone was not present or observable, the right side was substituted.

Differences in frequencies and associations of TB indicators with recorded TB diagnoses for the 18 skeletal indicators in the two collections were evaluated by χ^2 and Fisher's Exact tests. Disease diagnosis in samples of living and dead individuals is a probabilistic assessment based on disease indicator sensitivities and specificities (Table 2). True positives (TP) are individuals with the skeletal lesion of interest who also had TB according to the collection records. The *sick* individuals were from the Terry Collection, and all of them were said to have had had TB. True negatives (TN) are those who lacked the lesion and were free of the disease. All *not sick* were from the Bass Collection. They did not have TB listed in the collection records, and they were unlikely to have had unrecognized TB because of its low prevalence in late twentieth-century America. When a skeletal lesion's sensitivity is more than one minus its specificity, the probability of having the lesion is greater among individuals who actually had TB than those who did not have it (Boldsen, 2001). That is equivalent to saying the probability of the lesion is greater in people with TB than those without it when the sum of sensitivity and specificity exceeds one.

Table 2: Sensitivity and specificity diagnosis and lesion

	Diagnosis	
Lesion	Sick	Not sick
Present	True positive (TP)	False positive (FP)
Absent	False negative (FN)	True negative (TN)

$$sensitivity = \frac{TP}{\text{sick}}$$

$$specificity = \frac{TN}{\text{not sick}}$$

Table 3: Scoring criteria for 18 possible TB indicators.

Indicator	Scoring	Description
RIB1	Location	Visceral surface of all ribs examined.
	0:	No bone changes related to TB are present (Fig. 1).
	1:	Low nodules and a rough texture covering more than 5 cm (Fig. 1).
RIB2	Location	Visceral surface of all ribs examined.
	0:	No bone changes related to TB are present (Fig. 2.A. and 2.B.).
	1:	Two or more pieces of ribs larger than 5 cm have: • Superficial bone proliferation covering more than 5 cm (Fig. 2.A.). • One or more bean-shaped lytic lesions measuring more than 5 mm in diameter (Fig. 2.B.).
VER	Location	Cranial and caudal surfaces of all thoracic and lumbar vertebral bodies. Thoracic and lumbar vertebrae are recorded separately.
	0:	No bone changes related to TB are present (Fig. 3).
	1:	Clustered pits or deep cavities in one area measuring more than 10 mm (Fig. 3).
VEN1	Location	Ventral part of all thoracic and lumbar vertebral bodies. Thoracic and lumbar vertebrae are recorded separately.
	0:	No bone changes related to TB are present (Fig. 4).
	1:	Three or more large pits with a roughly circular shape and rounded edges each measuring at least 3 mm in diameter (Fig. 4). In severe cases there can be a large opening in the bone where the original trabecular structure has been destroyed (Fig. 4).
VEN2	Location	Ventral part of all thoracic and lumbar vertebral bodies. Thoracic and lumbar vertebrae are recorded separately.
	0:	No bone changes related to TB are present (Fig. 5).
	1:	Two or more thoracic or lumbar ventral surfaces have a proliferation of bone typically with a woven appearance that covers at least 50% of the bone's surface (Fig. 5).
BOD	Location	Lateral body of ilium between the lower gluteal line and upper acetabular margin.
	0:	No bone changes related to TB (Fig. 6).
	1:	One of the following is present: • Three or more large pits with a roughly circular shape and rounded edges each measuring more than 3 mm (Fig. 6). In severe cases an abscess can be present (Fig. 6). • A proliferation of bone with a woven structure is present on at least 50% of the bone's surface (Fig. 6).
ACE1	Location	Articular surface of the acetabulum.
	0:	No bone changes related to TB are present (Fig. 7).
	1:	Clustered pitting or large cavities occur on the articular surface in two or more areas, each measuring more than 3 mm, or in one area measuring more than 10 mm (Fig. 7). In severe cases there can be extensive bone destruction (Fig. 7).
ACE2	Location	Acetabular fossa of acetabulum.
	0:	No bone changes related to TB are present (Fig. 8).
	1:	Two or more deep cavities in the acetabular fossa, each measuring more than 3 mm or covering more than 50% of the area, with borders having the appearance of a woven structure with dense trabeculae (Fig. 8).
PF1	Location	Head of the femur.
	0:	No bone changes related to TB are present (Fig. 9).

	1:	Clustered pits or cavities occur on the femoral head in two or more areas, each measuring more than 3 mm, or in one area measuring more than 10 mm (Fig. 9).
PF2	Location	Greater trochanter of the proximal femur.
	0:	No bone changes related to TB are present (Fig. 10).
	1:	Clustered pits or large cavities on the greater trochanter occur in two or more areas, each measuring more than 3 mm, or in one area measuring more than 10 mm (Fig. 10).
ILI	Location	Iliac auricular surfaces.
	0:	No bone changes related to TB are present (Fig. 11).
	1:	Clustered pits (Fig. 11) or large cavities (Fig. 11) in two or more areas, each measuring more than 3 mm, or in one area measuring more than 10 mm.
DF	Location	Articular surface of the distal femur.
	0:	No bone changes related to TB are present (Fig. 12).
	1:	Clustered pits or cavities are present in two or more areas, each measuring more than 3 mm (Fig. 12), or in one area measuring more than 10 mm (Fig. 12).
PT1	Location	Articular surface of the proximal tibia.
	0:	No bone changes related to TB are present (Fig. 13).
	1:	Clustered pits or large cavities occur on the articular surface in two or more areas, each measuring more than 3 mm (Fig. 13), or one area measuring more than 10 mm (Fig. 13).
PT2	Location	Intercondylar area of the proximal tibia.
	0:	No bone changes related to TB are present (Fig. 14).
	1:	Three or more large pits are present in the intercondylar area, each measuring more than 3 mm (Fig. 14), or there is a proliferation of bone with a woven appearance (Fig. 14) that has spread across at least 50 % of intercondylar area. Bone destruction and proliferation can occur in the same specimen.
DH1	Location	Condylar area of the distal humerus.
	0:	No bone changes related to TB are present (Fig. 15).
	1:	Clustered pits covering more than 1 cm^2 are present on the posterior condylar portion of the humerus on the lateral, medial, or both sides (Fig. 15).
DH2	Location	Articular surface of the distal humerus.
	0:	No bone changes related to TB are present (Fig. 16).
	1:	Clustered pits or large cavities occur in two or more areas on the articular surface, each measuring more than 3 mm, or in one area measuring more than 10 mm (Fig. 16).
PR	Location	Radial tuberosity of the proximal radius.
	0:	No bone changes related to TB are present (Fig. 17).
	1:	Clustered pits or large cavities are present in two or more areas, each measuring more than 3 mm, or in one area exceeding 10 mm (Fig. 17).
PU	Location	Olecranon process of proximal ulna.
	0:	No bone changes related to TB are present (Fig. 18).
	1:	Clustered pits (Fig. 18) or large cavities (Fig. 18) are present on the olecranon process in two or more areas, each measuring more than 3 mm, or in one area measuring more than 10 mm.

3. Skeletal Scoring

Recording criteria for the 18 possible TB indicators are described in Table 3 and Figures 1-18. Criteria for distinguishing between the scores 0 (absent) and 1 (present) were designed to ensure detection of early stage skeletal involvement. The TB bony lesions depicted in the literature are

often advanced stages of the disease's progress, leaving initial pathological changes poorly described (Ortner, 2003; Roberts and Buikstra, 2003:127). As many of the potential TB indictors might be early stage skeletal manifestations of the disease, they often have no exact parallels in the published literature. Those indicators, however, are found in locations where skeletal lesions indicative of TB have been reported.

3.1. Rib Visceral Surface (RIB1 and RIB2)

The normally smooth visceral surface of ribs can be the site of bony changes attributed to TB or other respiratory diseases. Rib involvement has been discussed in clinical studies (Brown, 1980; Chang et al., 1999; Grover et al., 2011; Keny, 2014), as well as evaluations of modern skeletal reference collections (Kelley and Micozzi, 1984; Matos and Santos, 2006; Roberts et al., 1994; Santos and Roberts, 2001, 2006) and archaeological remains (Lambert, 2002; Lewis, 2011; Mays et al., 2002; Milner and Smith, 1990; Nicklisch et al., 2012; Pfeiffer, 1991; Raff et al., 2006).

Visceral surface of ribs (RIB1). Low nodules are located along the costal groove on the visceral surface of ribs. They are part of a proliferation of bone that takes on a rough or undulating appearance (Table 3; Fig. 1). These bony reactions are found in skeletons in the Human Identified Skeletal Collection at the Museu Bocage in Lisbon that were from individuals who had died of pulmonary TB (Matos and Santos, 2006).

Visceral surface of ribs (RIB2). These bony changes on ribs are characterized by a thin layer of bone proliferation, one or more osteolytic bean-shaped lesions, or both (Table 3; Fig. 2.A. and 2.B.). Adjacent ribs are often affected. The addition of bone can occur as a patch of woven bone indicative of its active formation at the time of death, or it can take on the relatively smooth-surfaced appearance of a pathological involvement that had healed earlier in life. Oval osteolytic lesions can be isolated or occur near one another, sometimes with several clustered together. They typically have smooth borders except where trabeculae are exposed in their deepest extent. These forms of pathological bony involvement could result from hematogenous pathogen dissemination or direct contact with sites of infection that might include intercostal lymph nodes (Harisinghani et al. 2000; Kelley and El-Najjar, 1980; Wiebe and Elwood, 1991).

Figure 1. RIB1 indicator: without changes, archaeological specimen (left); nodules, archaeological specimen (middle); and a large area with nodules, archaeological specimen (right).

Figure 2.A. RIB2 indicator: without changes, archaeological specimen (left); loosely adherent superficial woven bone proliferation, Terry Collection 13R (middle); and superficial bone proliferation, Terry Collection 592 (right).

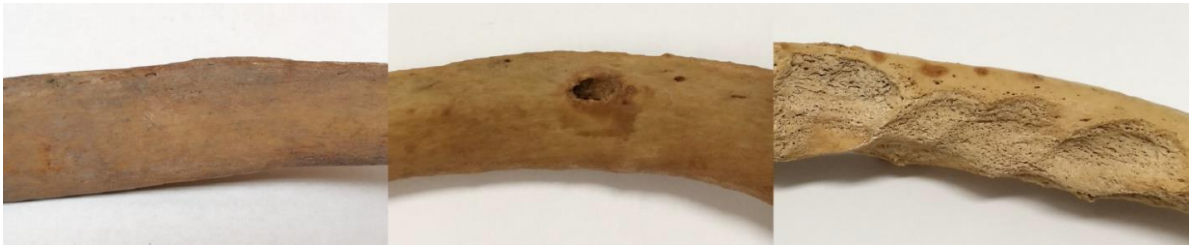

Figure 2.B. RIB2 indicator: without changes, archaeological specimen (left); deep osteolytic bean-shaped pit exposing underlying, but thickened, trabeculae, Terry Collection 1002 (middle); and shallow osteolytic pits, Terry Collection 1106 (right).

3.2. Spine (VER, VEN1 and VEN2)

The spine is a common site of TB-related skeletal changes (Garg and Somvanshi, 2013), as shown by numerous clinical (Maurya et al., 2016; Turgut, 2001; Wang et al., 2016) and archaeological studies (Hajdu et al., 2012; Kelley and El-Najjar, 1980; Resnick and Nawayama, 1995). The lower thoracic and upper lumbar regions are most frequently involved (Jain et al., 1993; Maurya et al., 2016; Turgut, 2001). Usually at least two adjacent vertebral bodies are affected (Jain et al., 1993; Kastert and Uehlerger 1964:486). Three different bony reactions on either thoracic or lumbar vertebrae are scored: cavitation of the cranial and caudal surfaces of vertebral bodies (VER), and either large pits (VEN1) or bone proliferation (VEN2) on the ventral aspects of vertebral bodies.

Cranial and caudal surfaces of thoracic and lumbar vertebral bodies (VER). Bony changes on these surfaces are characterized as pitting and cavitation (Table 3; Fig. 3). Such changes have been associated with TB (Aufderheide and Rodriquez-Martin, 1998:134-136; Jain et al., 1993; Ortner, 2003:231; Turgut et al., 2017). In adjacent vertebrae they are said to arise by direct extension through perforated intervertebral discs or through the vascular supply to vertebral bodies (Aufderheide and Rodriguez-Martin, 1998:122; Ortner, 2003:231). In severe cases, bony involvement can result in vertebral body collapse and subsequent spinal kyphosis (Morse, 1967; Rajasekaran, 2013). These changes should be distinguished from Schmorl's nodes that are found centrally on intervertebral surfaces and, in contrast to TB-related lesions, trabeculae tend not to be exposed within the depression (Sajula et al. 1986; Sonne-Holm et al., 2013).

Ventral part of vertebral bodies (VEN1). Large holes with a roughly circular shape and rounded edges that penetrate the cortical bone of the ventral surfaces of thoracic and lumbar vertebral bodies are readily visible in some individuals (Table 3; Fig. 4). Such skeletal changes have been characterized as cloacae produced in the central part of vertebral bodies (Ortner, 2003), and they might be an early sign of infection (Baker, 1999). The changes should not be confused with sharp-edged and irregular-shaped pits found on the lateral and ventral vertebral bodies of children and young adults that are related to normal bone development (Baker, 1999; Roberts and Buikstra, 2003:127).

Ventral part of vertebral bodies (VEN2). A proliferation of bone can occur on the ventral part of thoracic and lumbar vertebral bodies (Table 3; Fig. 5) (Kelley and El- Najjar, 1980; Baker, 1999; Haas et al., 2000; Ortner, 2003:232-234). It is likely a response to direct dissemination from an overlying paravertebral abscess (Maurya et al., 2016; Ortner, 2003:232; Tuli, 2010:204-207).

Figure 3. VER indicator: without changes, Terry Collection 1351 (left); clustered pits and cavities, Terry Collection 279 (middle); and large cavities, Terry Collection 1124R (right).

Figure 4. VEN1 indicator: without changes, Terry Collection 1351 (left); large circular to oval pits with rounded edges, Terry Collection 660 (middle); and large pits with some peripheral reactive bone, Terry Collection 1285 (right).

Figure 5. VEN2 indicator: without changes, Terry Collection 1351 (left); slight bone proliferation, Terry Collection 1468 (middle); and extensive bone proliferation that takes on a woven appearance, Terry Collection 1407 (right).

3.3. Hip joint (ACE1, ACE2, PF1 and PF2)

Lesions in the vicinity of the hip are a feature of some TB infections (Kelley and El-Najjar, 1980; Ortner, 2003:235-237; Saraf and Tuli, 2015; Tuli, 2010:69). Bony changes on the lateral body of the ilium adjacent to the acetabulum (BOD), in the acetabulum (ACE 1 and ACE2), and on the proximal end of femur (PF1 and PF2) are scored.

Lateral body of ilium (BOD). A pathological involvement of the lateral body of the ilium immediately adjacent to the acetabulum, resulting in the loss or addition of bone, is scored (Table 3; Fig. 6). Such lesions might represent drainage channels or secondary bony proliferation from extensions of a psoas abscess (Ortner, 2003:239). In advanced cases, an abscess can be present within the bone **(**Roberts and Buikstra 2003:93).

Articular surface of acetabulum (ACE1). Areas of pitting and cavities, which can sometimes

be several millimeters or more in diameter, on the articular surface of the acetabulum are scored (Table 3; Fig. 7). The bony changes arise from hematogenous dissemination or a direct extension from soft tissue paravertebral and psoas abscesses (Aufderheide and Rodriquez-Martin, 1998:139; Ortner, 2003:236; Tuli, 2010:69).

Acetabular fossa (ACE2). The cartilage-free portion of the acetabulum, the acetabular fossa, can be the site of osteolytic lesions several millimeters or more in diameter that are typically bordered by coarse trabeculae with minimal, if any, surrounding reactive bone formation (Table 3; Fig. 8). This non-articular part of the acetabulum is presumably involved through hematogenous dissemination or direct extension from elsewhere in the hip (Aufderheide and Rodriquez-Martin, 1998:138-139; Ortner, 2003:235-239).

Head of the proximal femur (PF1). Pitting and cavities on the femoral head can be a result of TB (Tuli, 2010:70). In severe cases, much or all of the head can be destroyed, resulting in a dislocation of the joint (Ortner, 2003:238; Tuli, 2010:82).

Greater trochanter of the proximal femur (PF2). The greater trochanter can be the site of bony changes attributed to TB (Ortner, 2003:239-240; Tuli, 2010:69). It is, however, considered the least common site in the hip joint for bony changes related to TB (Ortner, 2003:239; Tuli, 2010:70). Pitting in this area is scored as present (Table 3; Fig. 10).

Figure 6. BOD indicator: without changes, archaeological specimen (upper left); large rounded pits, Terry Collection 1072 (upper right); pits, Terry Collection 1331 (lower left); and bone proliferation, Terry Collection 1278 (lower right).

Figure 7. ACE1 indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 1531 (middle); and deep cavities, Terry Collection 1331 (right).

Figure 8. ACE2 indicator: without changes, archaeological specimen (left); deep pits, Terry Collection 1458 (middle); and deep cavities and woven structure, Terry Collection 980 (right).

Figure 9. PF1 indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 1222 (middle); and clustered pits and larger cavities, Terry Collection 1264 (right).

Figure 10. PF2 indicator: without changes, archaeological specimen (left); large pits and clustered pits, Terry Collection 207 (middle), and clustered pits, Bass Collection 08-03D (right).

3.4. Sacroiliac joint (ILI)

The sacroiliac joint is a common site of TB skeletal involvement (Aufderheide and Rodriquez-Martin, 1998:139; Ortner, 2003:237-239, Tuli, 2010:167-171). Bony changes possibly attributable to TB on the iliac auricular surface (ILI) are scored.

Iliac auricular surface (ILI). Irregular perforations of the joint surface, exposing underlying trabecular bone, can be present on the iliac auricular surface that, in aggregate, cover much of the joint (Table 3; Fig. 11). They should not be confused with surface defects commonly seen in the iliac side of the joint. The latter, which are not related to TB, can be deep, typically have rounded borders, and are often linear.

Figure 11. ILI indicator: without changes, archaeological specimen (left); clustered pits and deep cavities, Terry Collection 1419 (middle); and extensive cavities that cover most of the joint surface, Terry Collection 1205 (right).

3.5. Knee joint (DF, PT1 and PT2)

A tuberculous involvement of the knee is believed to often start as an infection of the synovial joint, it takes the form of a pitting and destruction of bone beneath the hyaline cartilage, and it can be

peripherally located where the capsule attaches to the femur and tibia. (Kelley and El-Najjar, 1980; Ortner, 2003:240; Tuli, 2010:111). Lesions are scored in both the distal femur (DF) and proximal tibia (PT1 and PT2).

Articular surface of the distal femur (DF). Pitting or large cavities occur on the articular surface of the femur (Table 3; Fig. 12) (Lidder et al., 2009; Tuli, 2010:124; Uboldi et al., 2017).

Articular surface of the proximal tibia (PT1). Pitting and cavities can appear on the proximal tibia much like they do on the femur (Table 3; Fig. 13) (Lidder et al., 2009; Ortner, 203:240; Tuli, 2010:111-112).

Intercondylar area of the proximal tibia (PT2). Large pits, sometimes accompanied by a proliferation of bone, can occur on the non-articular intercondylar area of the proximal tibia (Table 3; Fig. 14).

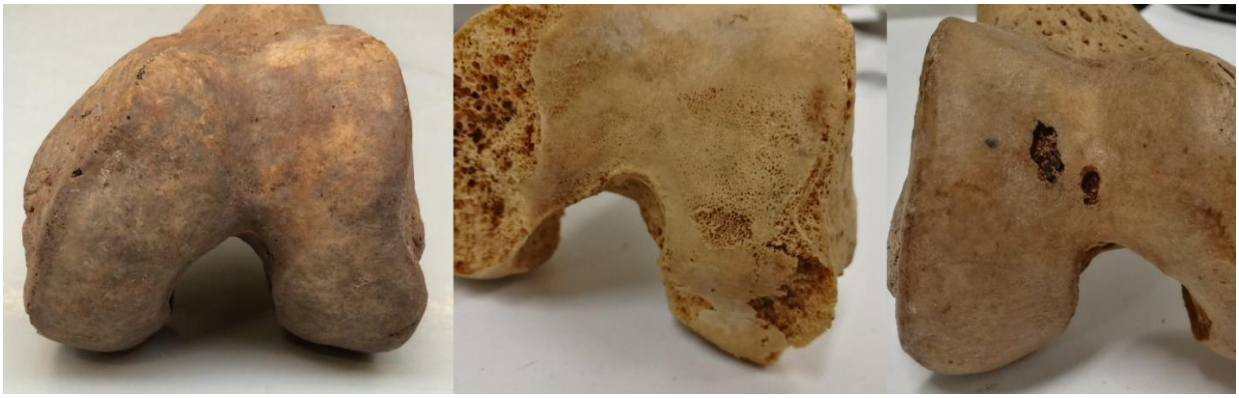

Figure 12. DF indicator: without changes, archaeological specimen (left); clustered pits and large cavity within the joint, Terry Collection 820R (middle); and deep cavities, Terry Collection 1315 (right).

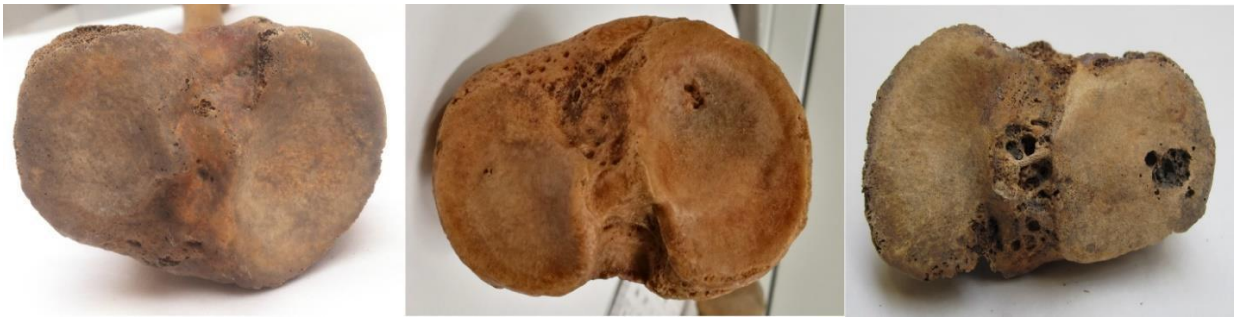

Figure 13. PT1 indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 309 (middle); and deep cavities, archaeological specimen (right).

Figure 14. PT2 indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 309 (middle); and deep cavities, Terry Collection 725 (right).

3.6. Elbow joint (DH1, DH2, PR and PU)

In the upper limb, the elbow is a frequent site of TB involvement (Ortner; 2003:243; Tuli, 2010:149). Bony changes are often seen first in the olecranon process or the distal humerus (Tuli, 2010:149). The distal humerus (DH1 and DH2), proximal radius (PR), and olecranon process of the proximal ulna (PU) are scored.

Condylar area of the distal humerus (DH1). Pitting, which can be extensive, in the medial and lateral condylar areas of the distal humerus is scored (Table 3; Fig. 15). In advanced cases, large and deep cavities can form (Ortner, 2003:245; Tuli, 2010:149-150).

Articular surface of the distal humerus (DH2). When the initial site of infection is the synovial joint, bony changes including pitting and deep cavities can occur on the articular surface of humerus (Table 3; Fig. 16) (Ortner, 2003:243-245; Tuli, 2010:149).

Radial tuberosity of the proximal radius (PR). The proximal end of radius is a site of infrequent bone involvement (Ortner, 2003:243-245; Sever, 1910; Tuli, 2010:149). Pitting and cavities on the radial tuberosity are scored (Table 3; Fig. 17).

Olecranon process of proximal ulna (PU). The proximal ulna, including the olecranon process, can be a site of TB involvement, although the joint itself is infrequently affected (Dhillon et al., 2012; Kelley and El-Najjar, 1980; Ortner, 2003:243; Sever, 1910; Sorrel and Sorrel-Dejerine, 1932:121). Pitting, usually bordered by relatively smooth-surfaced bone, is scored (Table 3, Fig. 18).

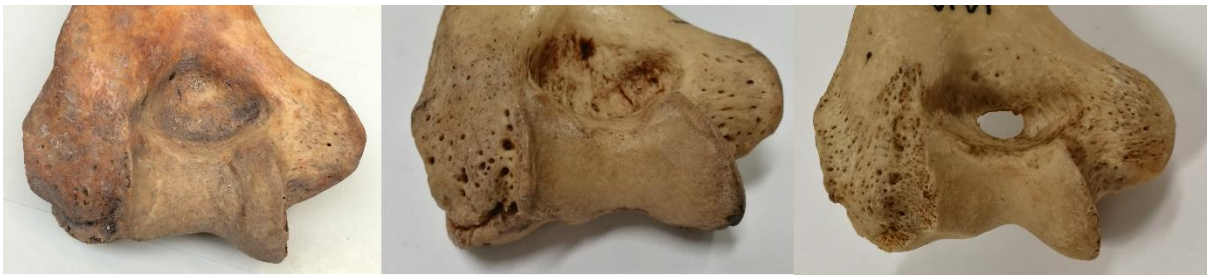

Figure 15. DH1 indicator: without changes, archaeological specimen (left); pits on the lateral condyle, Terry Collection 1315 (middle); and extensive pitting on the lateral condyle, Terry Collection 1419 (right). The septal aperture in the right image is not associated with pathological processes.

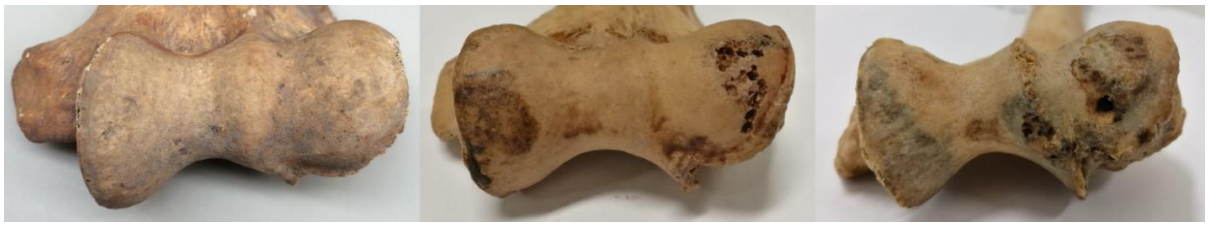

Figure 16. DH2 indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 1315 (middle); and clustered pits and large cavities, Terry Collection 626 (right).

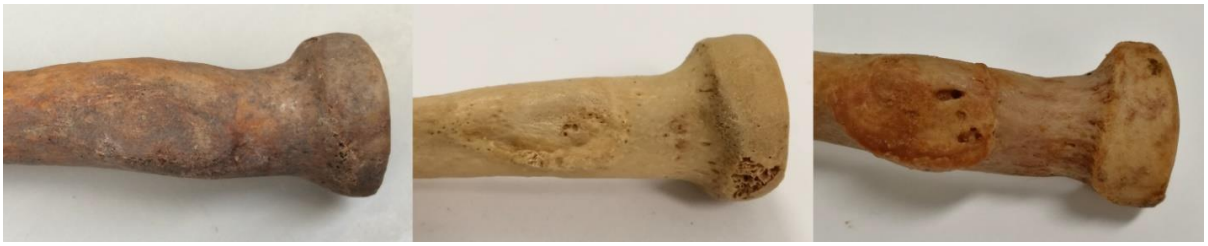

Figure 17. PR indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 1419 (middle); and cavities, Terry Collection 1453 (right).

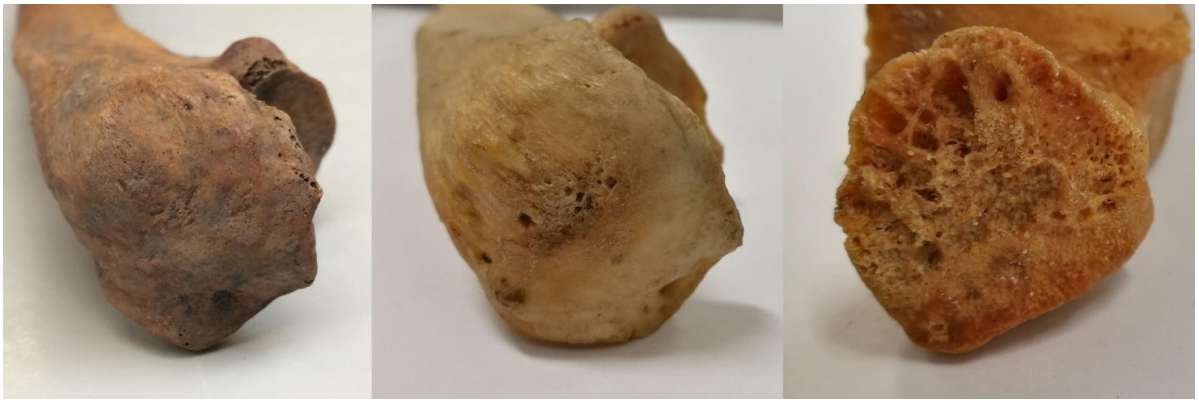

Figure 18. PU indicator: without changes, archaeological specimen (left); clustered pits, Terry Collection 799 (middle); and clustered pits and large cavities, Terry Collection 820R (right).

4. Results

The most common skeletal lesion in the Terry Collection TB cases is a proliferation of bone on the ventral vertebral bodies (VEN2), with just over one-half of the individuals affected (Table 4). The least common candidate indicator is the proximal tibia articular surface (PT1). Of the Bass controls, many of whom were probably not even exposed to the pathogen at any point in their lives, 139 have visceral rib nodules designated RIB1. This particular skeletal lesion, and PF2 on the femoral greater trochanter, are more common in the Bass controls than in the Terry cases. For the remaining candidate indicators, the Terry skeletons are affected more often than the Bass skeletons. No Bass skeleton has the proximal tibia lesions PT1 and PT2, or those designated DH1 and DH2 on the distal humerus.

Differences between case and control frequencies are statistically significant at the $p < 0.05$ level for 10 of the 18 skeletal indicators (Table 4). For nine of these indicators the frequencies of affected individuals in the TB cases exceeds those of the controls. That indicates for those nine an association between the particular kind of skeletal involvement and a positive disease diagnosis. The remaining eight indicators cannot be considered useful for diagnostic purposes based on the size and composition of the current skeletal sample, and the ways in which they are scored.

Table 4: Eighteen candidate skeletal indicators for TB in the Terry (N=240) and Bass (N=240) collections. Scoring criteria for the indicators are listed in Table 3. The p values are from Fisher's Exact tests.

Lesion		Terry Collection		Bass Collection		p values
		N	%	N	%	
RIB1	Unaffected	144	60.0	99	41.6	<0.001
	Affected	96	40.0	139	58.4	
RIB2	Unaffected	159	66.3	236	99.7	<0.001
	Affected	81	33.7	3	1.3	
VER	Unaffected	219	91.3	228	95.0	0.148
	Affected	21	8.7	12	5.0	
VEN1	Unaffected	190	79.2	234	97.9	<0.001
	Affected	50	20.8	5	2.1	
VEN2	Unaffected	112	46.7	228	95.4	<0.001
	Affected	128	53.3	11	4.6	
BOD	Unaffected	159	66.8	225	97.8	<0.001
	Affected	79	33.2	5	2.2	
ACE1	Unaffected	225	94.5	231	99.6	0.002
	Affected	13	5.5	1	0.4	
ACE2	Unaffected	138	58.0	215	93.5	<0.001
	Affected	100	42.0	15	6.5	
PF1	Unaffected	229	96.6	228	98.7	0.221
	Affected	8	3.4	3	1.3	
PF2	Unaffected	233	98.7	221	96.9	0.214
	Affected	3	1.3	7	3.1	
ILI	Unaffected	162	70.4	210	94.2	<0.001
	Affected	68	29.6	13	5.8	
DF	Unaffected	234	97.9	227	99.1	0.450
	Affected	5	2.1	2	0.9	
PT1	Unaffected	237	99.6	230	100.0	1.000
	Affected	1	0.4	0	0.0	
PT2	Unaffected	233	97.9	230	100.0	0.061
	Affected	5	2.1	0	0.0	
DH1	Unaffected	229	96.6	234	100.0	0.007
	Affected	8	3.4	0	0.0	
DH2	Unaffected	232	97.9	234	100.0	0.061
	Affected	5	2.1	0	0.0	
PR	Unaffected	234	97.9	231	98.7	0.724
	Affected	5	2.1	3	1.3	
PU	Unaffected	217	90.8	230	98.3	<0.001
	Affected	22	9.2	4	1.7	

Table 5: χ^2-test results of the relationship of the 18 indicators.

	RIB2	VER	VEN1	VEN2	BOD	ACE1	ACE2	PF1	PF2	ILI	DF	PT1	PT2	DH1	DH2	PR	PU
RIB1	0.943	0.936	0.393	**0.040**	**0.046**	0.644	0.917	**0.035**	0.505	0.428	0.720	0.313	0.639	0.159	0.182	0.450	0.938
RIB2		0.709	**<0.001**	**<0.001**	**<0.001**	0.279	**<0.001**	0.404	0.135	**<0.001**	0.084	**0.033**	0.198	**0.017**	**0.013**	0.693	**0.005**
VER			0.056	**<0.001**	**0.032**	0.933	**0.006**	0.764	0.088	0.159	**0.022**	0.786	0.542	0.441	0.238	0.442	0.319
VEN1				**<0.001**	**<0.001**	0.236	**<0.001**	0.225	0.246	**0.002**	0.164	0.715	0.565	0.237	**0.001**	0.301	0.061
VEN2					**<0.001**	**0.004**	**<0.001**	0.240	0.986	**<0.001**	0.426	0.517	0.132	**<0.001**	**<0.001**	**0.037**	**0.001**
BOD						**<0.001**	**<0.001**	0.424	0.504	**<0.001**	0.473	0.637	0.916	**<0.001**	**<0.001**	0.149	**0.024**
ACE1							**<0.001**	**0.003**	0.586	0.606	0.637	0.860	0.691	**<0.001**	0.025	0.112	0.794
ACE2								0.373	0.706	**<0.001**	**0.048**	0.083	0.069	**0.013**	**<0.001**	0.095	**<0.001**
PF1									0.672	**0.016**	**<0.001**	0.876	0.009	**<0.001**	**0.009**	**<0.001**	0.608
PF2										0.854	0.728	0.882	0.738	0.671	0.738	**0.043**	0.544
ILI											0.465	0.033	**0.014**	**0.001**	**0.090**	**0.001**	**0.001**
DF												**<0.001**	**0.001**	**0.010**	**<0.001**	**0.010**	**0.008**
PT1													**<0.001**	0.895	0.917	0.895	0.808
PT2														**0.002**	0.815	0.766	**0.001**
DH1															**<0.001**	**<0.001**	**<0.001**
DH2																**0.001**	**<0.001**
PR																	0.381

Relationships among skeletal indicators evaluated through χ^2 tests are listed in Table (5). Non-significant indicators in Table 4 tend to be closely associated with fewer other indicators than the ones where the Terry and Bass frequencies are significantly different.

Sensitivity and specificity estimates for each skeletal indicator are provided in Table 6. The Estimate and sensitivity + specificity columns in Table 6 provide the diagnosis probabilities of interest. For all but two indicators, RIB1 and PF2, the sensitivity + specificity >1 criterion for being related to TB is met.

The following examples illustrate what the Estimate values in Table 6 indicate. A bony reaction on ventral vertebral bodies (VEN2) means there is a 53.3% probability of a true TB diagnosis (Sensitivity Estimate). When such lesions are absent, there is a 4.1% probability of TB (1 – specificity). In contrast, the PF2 femoral greater trochanter lesions, when present, only provide a 1.3% probability of TB diagnosis. When absent, there is a 3.1% probability of the individual having TB. There is a greater probability of having TB among individuals without PF2 than there is for those with it. That bony feature, therefore, is of no use when seeking to identify TB in skeletal samples.

Of all the possible TB indicators, 6 of 18 meet three criteria for a good marker of this disease (Table 7). They are found in significantly ($p< 0.001$) more of the Terry skeletons; they are significantly related to at least one-half of the other skeletal lesions; and the sensitivity measure exceeds 0.05.

Table 6: Sensitivity and specificity measures for the eighteen indicators.

Lesion	Sensitivity				Specificity				Sens + Spec
	Estimate	S.E.	95 % CI		Estimate	S.E.	95 % CI		
RIB1	0.400	0.0316	0.339	0.463	0.416	0.0319	0.355	0.479	0.816
RIB2	0.337	0.0305	0.280	0.399	0.987	0.0072	0.968	0.997	1.324
VER	0.088	0.0182	0.056	0.126	0.950	0.0141	0.917	0.973	1.038
VEN1	0.208	0.0262	0.160	0.263	0.962	0.0093	0.932	0.981	1.170
VEN2	0.533	0.0322	0.470	0.596	0.959	0.0136	0.922	0.976	1.492
BOD	0.332	0.0305	0.274	0.393	0.949	0.0096	0.912	0.972	1.281
ACE1	0.055	0.0147	0.030	0.088	0.996	0.0043	0.981	1.000	1.051
ACE2	0.420	0.0320	0.359	0.483	0.935	0.0163	0.898	0.962	1.355
PF1	0.034	0.0117	0.016	0.062	0.987	0.0074	0.967	0.997	1.021
PF2	0.013	0.0073	0.003	0.033	0.969	0.0114	0.941	0.987	0.982
ILI	0.296	0.0301	0.239	0.357	0.942	0.0157	0.906	0.968	1.238
DF	0.021	0.0093	0.008	0.044	0.991	0.0061	0.973	0.998	1.012
PT1	0.004	0.0042	0.000	0.018	0.999	0.0000	0.991	1.000	1.003
PT2	0.021	0.0093	0.008	0.045	0.999	0.0000	0.991	1.000	1.020
DH1	0.034	0.0117	0.016	0.062	0.999	0.0000	0.991	1.000	1.033
DH2	0.021	0.0093	0.008	0.045	0.999	0.0000	0.991	1.000	1.020
PR	0.021	0.0093	0.008	0.044	0.987	0.0074	0.967	0.997	1.008
PU	0.092	0.0187	0.060	0.133	0.983	0.0085	0.961	0.995	1.075

Table 7: Three criteria characterizing the association of 18 skeletal indicators and TB. Criteria not met marked with - and criteria met marked with X.

	Found mostly in Terry skeletons at p <0.001 (Table 4)	Significant relation with ≥9 other indicators (Table 5)	Sensitivity >0.05 (Table 6)
RIB1	-	-	X
RIB2	X	X	X
VER	-	-	X
VEN1	X	-	X
VEN2	X	X	X
BOD	X	X	X
ACE1	-	-	X
ACE2	X	X	X
PF1	-	-	-
PF2	-	-	-
ILI	X	X	X
DF	-	X	-
PT1	-	-	-
PT2	-	-	-
DH1	-	X	-
DH2	-	X	-
PR	-	-	-
PU	X	X	X

5. Discussion

5.1. Sample Composition

In previous studies of TB skeletal involvement, the general approach has been to compare individuals said to have had the disease to those in the same collection where the disease is not mentioned in the records. Examples of this work include those that used the Hamann-Todd and Terry collections from the United States (Kelley and El-Najjar, 1980; Kelley and Micozzi, 1984; Roberts et al., 1994), the Coimbra and Museum Bocage collections from Portugal (Matos and Santos, 2006; Santos and Roberts, 2001, 2006), the Certosa Cemetery Collection from Italy (Mariotti et al., 2015), and the Pretoria and Dart collections from South Africa (Steyn et al., 2013). There is a problem, however, with using the same reference collection for both sick people and individuals who were supposedly free of the disease. Considering when and where these people lived, many of those who were not listed as sufferers of TB, and possibly all of them, were exposed to *M. tuberculosis* complex bacteria at some point in their lives. That is because TB was widespread

in 18th to early-20th century North America, Europe, and Africa (Bates and Stead, 1993; Daniel, 2009; Madsen et al., 1942). It is likely that TB was not noted in the sparse documentation available on some individuals who had the disease with its accompanying skeletal lesions. A more immediate or obvious cause of death could have been reported, TB might not have been mentioned because of social stigma associated with acknowledging and reporting it, or the disease was not identified because diagnostic procedures were inexact and not always thorough. The extent to which unrecognized cases affect such skeletal studies remains unknown, indeed unknowable. It would not be surprising, however, if at least a few TB sufferers were included among the non-TB individuals identified through available records.

To take but one example, the association between rib lesions and TB was brought to the attention of paleopathologists through an influential study of skeletons selected because they were from people reported as having the disease (Kelley and Micozzi, 1984). A control group – individuals who supposedly did not have the disease – was not part of that study. The linkage between the rib lesions and the disease was subsequently examined in skeletons of people reported as having TB and those said to have died from other causes (Mariotti et al., 2015; Matos and Santos, 2006; Roberts et al., 1994). Three aspects of the follow-up studies are worth highlighting. The research was undertaken because of uncertainty associated with making diagnoses based on pathological bony indicators. This work, quite rightly, included individuals classified as not having TB, although sometimes they were reported as having had other pulmonary diseases. It was recognized that an unknown number of people who suffered from the disease could have been reported as non-TB deaths.

The present study was specifically designed to address the problem of using a single skeletal collection for both cases and controls. The non-sick were from a sample where TB prevalence in the living population was quite low. It is unlikely people who had TB slipped unrecognized into the non-TB category, reducing classification error. For clarification, what is of concern is not the people who are thought to have had TB, as long as records are deemed sufficient to identify individuals who actually had the disease instead of something else. The concern is instead with identifying people who did not have TB. That is where using a skeletal sample, such as the Bass Collection, comprised of individuals who were unlikely to have developed the disease is important.

5.2. Pathological Indicators

At the outset of a study such as this one, it is only necessary for there to be some reason why there might be an association between a skeletal indicator and the disease. It makes sense to identify as many potential indicators as possible before evaluating their diagnostic value because it can be expected that a number of indicators – in this study, the majority – will be eliminated during the assessment process. That might happen if the indicator is not associated with the disease of interest; it is a rare disease outcome, so it occurs infrequently, if at all, in the skeletal sample; or the scoring threshold is set incorrectly.

In this sample, 6 of 18 candidate bony indicators were associated with a TB diagnosis made when the individuals were alive. Each of the six indicators had to meet three stringent criteria to be accepted. The conservative approach is designed to yield estimates that would produce reliable results when incorporated into paleoepidemiological studies. The remaining 12 indicators, as they have been defined here, provide limited, if any, information about TB in analyses of archaeological skeletons.

The rib indicators serve as an example of how some bony features might be a good marker of a disease, whereas others on the same anatomical structure are not. Consistent with Kelley and Micozzi's (1984) pioneering work, it appears that a superficial proliferation of bone or bean-shaped

areas of bone loss (RIB2) are found more frequently in TB cases than in controls. Only two individuals in the control group have such lesions. Both are males, and they are reported as having had cancer, one unspecified and the other metastatic prostate cancer. Other parts of these two skeletons also exhibit a pathological proliferation of bone. The positive RIB2 scores in the two controls are presumably related to widespread bony involvement that can occur in metastatic cancer (Chen et al., 2003; Kakhki et al., 2013). The RIB1 indicator, in contrast, occurs more often in controls than in TB cases. It is likely a non-specific sign of chronic pulmonary conditions, as suggested previously by Eyler et al. (1996), Matos and Santos (2006), and Roberts et al. (1994). The small bony nodules are located superior to the costal groove, usually immediately adjacent to it, where they correspond to the attachment of the intercostalis internus muscles and their continuation by intercostal membranes. These muscles are involved in forceful expiration, as happens when coughing (Goss, 1973:415; Köpf-Maier, 2004:71). Chronic coughing can come about for several reasons, although for these individuals long-term and detailed medical histories are unavailable.

The three forms of vertebral involvement, VER, VEN1, and VEN2, highlight both this study's weaknesses and problems experienced when dealing with archaeological remains. TB cases and controls are significantly different for VEN1 and VEN2, but not VER. Although VER is not considered to be related to TB in this study, the lesions are generally regarded a sign of skeletal TB (Aufderheide and Rodriquez-Martin, 1998:134-136; Jain et al., 1993; Kelley and El-Najjar, 1980; Ortner, 2003:231; Turgut et al., 2017), and they have been interpreted as such in archaeological samples (Haas et al., 2000; Hajdu et al., 2012). The lack of association of VER and a TB diagnosis is presumably a result of the cutoff point used for scoring a positive lesion – it was set too low during data collection. There is no reason to doubt the weight of prior research on this matter. Instead, our findings result from an interest in detecting TB at an early stage. Apparently, many vertebral defects are scored as positive when they are not related to TB at all. That underscores problems faced when criteria for identifying skeletal lesions depart from highly distinctive, or classic, expressions of pathological processes.

Turning to the other two forms of vertebral involvement, both VEN1 and VEN2 are found significantly more often in TB cases than in controls, but the latter occurs in over twice as many skeletons as the former. For quantitative analyses of archaeological skeletons, it is reasonable to use VEN2, the more commonly occurring TB indicator. Moreover, bone proliferation is not as prone to misidentification as its loss, which is a consideration when dealing with poor bone preservation in archaeological contexts. That said, osteolytic lesions in the anterior portion of vertebral bodies, designated VEN1, are a recognized aspect of skeletal TB (Ortner, 2003:231, 233-236). With a larger skeletal sample, and perhaps a tighter indicator definition, more precise estimates of their frequency can be obtained that could prove useful in future work.

Both ACE1 and ACE2 are found significantly more often in TB cases than in controls. It is not surprising that the acetabular indicators are found to be associated with TB because, after the spine, the hip is generally the most commonly affected anatomical structure (Aufderheide and Rodriguez-Martin, 1998:124; Ortner, 2003:235; Tuli, 2010:69). Both the articular and non-articular parts of the acetabulum can be affected (Ortner, 2003:237), although the acetabular fossa (ACE2) is involved more than seven times as often as the lunate surface (ACE1).

The indicators PF1 and PF2 on the proximal femur are not related to TB, although the hip, including the femur, is often a site of TB involvement (Aufderheide and Rodriguez-Martin, 1998:124; Ortner, 2003:235). That is more of a surprise for the femoral head (PF1), considering what is found on the acetabulum, than it is for the greater trochanter (PF2). Perhaps PF1 is rare enough that a much larger sample is needed to detect its association with TB. In contrast, the greater trochanter PF2 lesion is unlikely to ever be a good indicator of TB, regardless of the size of the skeletal sample, because it occurs more often in controls than in TB cases. Tuberculous bursitis can

result in pathological changes to the greater trochanter, but the condition rarely occurs in modern clinical studies (Tayfur et al., 2015).

For the purposes of this study, and future work, the bones of the knee and elbow are of limited value. Interestingly, elsewhere the knee is said to be a reasonably common site of TB involvement (Aufderheide and Rodriguez-Martin, 1998:139; Tuli, 2010:111; Uboldi et al., 2017). Only PU, which involves the ulnar olecranon process, appears to hold any potential. That is consistent with clinical studies where this site is considered to be the most commonly affected part of the elbow (Dhillon et al., 2012; Sever, 1910). The remaining candidate indicators of TB in the knee and elbow joint either occur in roughly equal frequencies in cases and controls, or they are found in quite low numbers if they are significantly associated with the disease.

However useful any of the TB indicators might prove to be in quantitative analyses of TB prevalence in the past, this study would have been improved by a larger sample. It is too small for some indicators to occur in high enough frequencies to provide reliable estimates of their association with the disease. That requires doubling, tripling, or even quadrupling the size of the reference sample beyond what was examined in this proof-of-concept study. Moreover, rarely occurring TB indicators, even if good estimates can be generated from enormous reference collections, would have little value when examining most archaeological samples, which are generally rather small, rarely numbering more than a few hundred well-preserved skeletons. The study also would have been improved if some skeletal features were redefined, notably VER that would benefit from more restrictive criteria for positive scores. Doing that for VER, however, would reduce the number of positive scores, returning us again to the need for much larger samples. Thus, this study is best regarded as a first step towards acquiring the information needed for paleoepidemiological studies of the prevalence of TB in archaeological samples. That, in turn, is an essential component of quantitative assessments of the disease's impact on past communities (Milner and Boldsen, 2017).

All classifications are affected by how the phenomena of interest are defined. In this instance, low cutoff points increase false positives, while they minimize false negative assessments. High cutoff points, such as the use of classic skeletal lesions, result in fewer false positives, but there are many more false negatives. Either way, it is difficult to interpret sick and non-sick frequencies if skeletons are assessed individually as having to belong to one or the other categories. One strength of this study is the uncertainty between the bony indicator and a disease – that is, the strength of the relationship between the two – is explicitly and quantitatively accommodated by specificity and sensitivity estimates.

Before leaving the subject of disease indicators, the issue of bilateral traits deserves attention because how they are handled has an effect on the results (Milner and Boldsen 2017). Here only scores from one side of the body were used for the Terry and Bass reference samples. That was done in the simplest way possible: selecting the left side, and substituting the right when the left was unobservable. A problem with bilateral traits arises from the ever-present possibility of incomplete observations. For any given candidate indicator, some skeletons might lack one of the two sides because bones are missing or damaged. That means some skeletons will have two opportunities for a positive disease indicator score, but others have only one because either the right or left side is not observable. Having a fixed procedure established in advance whereby all skeletons are treated equally is essential in quantitative, as opposed to descriptive, paleopathological studies.

5.3. Disease Prevalence

In one respect – its probabilistic nature – the estimation of disease prevalence in skeletal samples is similar to using bony indicators in individual skeletons to identify the presence of specific diseases.

That is precisely why a differential diagnosis approach has been the cornerstone of paleopathological research for over forty years (Buikstra, 1976). Estimates of sensitivity and specificity for various skeletal features, some more indicative of a particular disease than others, move such probabilistic assessments from individual skeletons to entire archaeological samples. From there, it is possible to begin the process of estimating the impact of various diseases on past communities.

This study is structured around probabilistic assessments of frequencies in skeletal samples using an array of indicators. Here, the bony indicators must have a positive relationship with the disease of interest; that is, sensitivity must exceed one minus its specificity (Boldsen, 2001). It would be nice to have skeletal lesions that are tightly associated with specific diseases, but they are not essential. That is why estimates of disease prevalence in archaeological samples should be derived from estimates of true positives and true negatives. Here attention is directed toward estimating disease prevalence in samples of skeletons. An individual skeleton is of little concern, except that it contributes to the sample used in quantitative analyses of past communities. It is easier to estimate disease prevalence in a skeletal sample than it is to specify precisely which individual was indeed sick. Exceptions are the few skeletons with highly distinctive, or classic, bony lesions. They would often be from people who had experienced a protracted illness where the characteristic lesion size, shape, and distribution had time to develop. But not all long-suffering individuals would have followed the same, or even a typical, disease course with regard to the involvement of bones, as is recognized for TB (Ortner, 2003:230).

Three limitations of the present study should be acknowledged. First, infrequently occurring lesions, such as those on the cranium, in the shoulder, head and neck of ribs, and hands and feet (Aufderheide and Rodriquez-Martin, 1998; Ortner, 2003; Roberts and Buikstra, 2003), are not included. These skeletal lesions might well have diagnostic value, but in studies based on only a few hundred skeletons, such as this one, they are unlikely to occur often enough to be of practical significance. That is also likely true of some of the skeletal indicators examined here that are subsequently dismissed from further consideration. Second, this investigation focused on adults for the simple reason that their skeletons were available for examination. Skeletal lesions often found in children can be examined in a similar manner if enough juveniles can be found to serve as TB cases and controls. Third, the estimates generated through this study are only useful to the extent that the disease's progress, at least in terms of recognizable skeletal lesions, was much the same in the distant past as it was in the near-recent pre-antibiotic period. For TB, the situation becomes more complicated because there are different forms of the disease. The TB cases in this study were drawn from the Terry Collection, and most, if not all, of these individuals had pulmonary TB. That is consistent with the considerable rib involvement, as is also true of other studies where modern reference samples have been examined (Kelley and Micozzi, 1984; Mariotti et al., 2015; Matos and Santos, 2006; Roberts et al., 1994; Santos and Roberts, 2001, 2006). There is proportionately more extra-pulmonary involvement in populations with high rates of infection with *M. bovis* (Cormican and Flynn, 1992). A greater degree of involvement of joints might well occur in such populations, and that would affect estimates of sensitivity and specificity for various disease indicators. For TB, that issue will be difficult to address with well-documented skeletal collections because they tend to be made up of individuals from times and places where pulmonary TB predominated.

However important estimating disease prevalence in a group of skeletons might be, it is not the same as doing so for a once-living population (Milner and Boldsen, 2017). The latter is what is of most interest when characterizing life in past communities. Skeletal lesions resulting from diseases acquired during an individual's lifetime, assuming the illnesses were associated with an increased risk of dying, will be overrepresented in mortality samples relative to what they were in the living populations from which they were drawn (Milner and Boldsen, 2017; Wood et al., 1992).

An example of such a disease is TB. On the other hand, a focus only on skeletal lesions that are highly distinctive of specific diseases will underestimate the people who contracted those particular diseases (Dutour, 2008; Milner and Boldsen, 2017). Relatively few people with TB tend to have skeletal lesions in the first place, so TB sufferers will be underestimated when only dry bones are available for examination (Ortner, 2003:228; Roberts and Buikstra, 2003:127; Steinbock, 1976:175). One cannot assume that the opposing tendencies cancel one another out, allowing straightforward interpretations about past populations from counts of skeletons with one or more distinctive bony lesions.

Progress is being made in moving from skeletons to once-living populations, although procedures for doing so have yet to be fully worked out (Milner and Boldsen, 2017; Usher, 2000). They involve estimating the risk of dying associated with particular pathological conditions, and that is by no means easy to do (Milner and Boldsen, 2017; Wood et al., 1992).

In clinical settings, sensitivity and specificity are not the only means of expressing the efficacy of diagnostic tests. One can also refer to negative or positive predictive values. Sensitivity and specificity are related to the biology of the disease. Predictive values, although based on an indicator's sensitivity and specificity, also take the disease's known or estimated population prevalence into account (Kirkwood and Sterne, 2003). These values are estimates of the probability that a patient is truly positive or negative if the test results are positive or negative, respectively. In the present study, the association of various skeletal lesions and TB was of interest, so the concern is with sensitivity and specificity to assess an indicator's capacity to detect the disease. Predictive values would come into play if there was some other information concerning prevalence in either the mortality sample or the once-living population.

6. Conclusion

The identification of highly distinctive lesions, eliminating alternatives through differential diagnosis, is quite useful when the objective is determining whether a particular disease happened to be present in a specific time and place (Buikstra, 1976). Tallies of skeletons with classic expressions of a disease, however, will do nothing to help estimate disease prevalence in the past, one of the principal objectives of paleoepidemiology (Milner and Boldsen, 2017). Establishing how common that disease happened to be is an essential part of assessing its impact on past communities. Tackling such a question requires a broad array of skeletal indicators, each with its estimated sensitivity and specificity. While both objectives – demonstrating that a disease was present and estimating its prevalence – are necessary components of furthering our understanding of life many centuries or millennia ago, they require distinctly different approaches to the study of archaeological skeletons.

In this study we present quantitative estimates of the association between specific pathological indicators on dry bones and TB, a disease that has ravaged human populations for thousands of years. We derive the sensitivity and specificity estimates from a sample that differs in one important respect from previous studies of TB lesions in modern reference collections. Here the non-sick are drawn from a different sample than the sick, not the same skeletal collection. Taking the non-sick from a sample comprised of people who were living at a time when the disease was uncommon reduces the risk of misclassifying people who actually had TB (sick) as individuals who did not have TB (not sick).

The inexact relationship between bony indicators and particular diseases is precisely why sensitivity and specificity estimates are needed when assessing the disease experience of prehistoric and historic-period communities (Boldsen, 2001; Milner and Boldsen, 2017). The figures provided here for six skeletal lesions can be used to estimate the prevalence of TB in archaeological samples.

That is particularly true if there is reason to believe pulmonary TB was the primary form of the disease that affected the population.

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