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Differential survival among individuals with active and healed periosteal new bone formation

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ABSTRACT

Periosteal new bone formation is frequently used in paleopathological and paleoepidemiological studies to diagnose particular diseases or to assess non-specific stress in past populations. Many researchers distinguish between active (woven or unremodeled) and healed (sclerotic or remodeled) periosteal lesions during data collection, but few published studies maintain a distinction between these two activity categories in analysis or interpretation. Though it has been suggested that healed periosteal lesions might indicate relatively good health and enhanced survivorship, no study has explicitly examined this possible relationship in a large skeletal sample that includes both children and adults. This study examines the relationship between periosteal lesion activity (active vs. healed) and survival using a sample of 538 individuals from several medieval London cemeteries, which in combination span the period 1120–1538. The results of Kaplan–Meier survival analysis indicate that healed periosteal lesions are associated with survival advantages compared to both those with active lesions and those without any lesions at all. These results suggest that active periosteal lesions might most closely reflect high frailty and bioarchaeological studies should focus on the distinction between the presence or absence of *healing* rather than merely on the presence of periosteal lesions irrespective of their activity.

1. Introduction

Periosteal new bone formation (i.e. periosteal lesions) is a proliferative skeletal lesion that occurs in response to stimuli that tear, stretch, compress or otherwise traumatize the periosteum, and as a result of local or systemic infection or inflammation associated with a variety of factors (Larsen, 1997; Ortner, 2003; Weston, 2008). Though typically viewed by bioarchaeologists as a marker of traumatic injury or an infection, periosteal new bone formation can occur as a result of a nutritional imbalance (Huss-Ashmore et al., 1982; Paine and Brenton, 2006); for example, localized hemorrhages resulting from vitamin C deficiency can lead to the proliferation of new bone (Geber and Murphy, 2012; Roberts and Manchester, 2005). Periosteal lesions are also associated with neoplastic, metabolic, congenital, and genetic diseases (Chen et al., 2012). New bone formation ultimately occurs because of the activity of osteoblasts, and disease, injury, or other factors that result in an increase in vascular permeability and edema can create conditions that are favorable to osteoblast activity (e.g. providing the material necessary for bone matrix production) (Ragsdale and Lehmer, 2012). Damage to the periosteum can result in blood seeping from associated blood vessels and subsequent hematoma formation, and this triggers inflammatory responses that can lead to the formation of new bone (Bastian et al., 2011). Though inflammation – which is the body's response to physical or chemical damage, invasion by pathogens, and other harmful stimuli – can interfere with bone formation by downregulating osteoblast activity and promote bone resorption by increasing osteoclast activity, some pro-inflammatory mediators do promote new bone formation (Thomas and Puleo, 2011). For example, the pro-inflammatory cytokines IL-1β and TNF-α and β can stimulate osteoblastic proliferation and the production of mineralized bone matrix (Frost et al., 1997; Lange et al., 2010). Some pro-inflammatory mediators cause vasodilation (DeFranco et al., 2007), and increased blood flow at the site of inflammation can result in periosteal hyperplasia and thus new bone formation (Walton and Rothwell, 1983). In addition to being influenced by inflammatory factors, the formation of periosteal new bone is affected by hormones and other signaling molecules (Dimitriou et al., 2005; Weston, 2012). The multiple etiologies and the interaction of various factors involved in periosteal new bone formation complicate its interpretation in bioarchaeological research; nevertheless, bioarchaeologists

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often assess periosteal lesions when reconstructing health in the past.

Periosteal lesions are often used by bioarchaeologists as non-specific indicators of physiological stress in response to endogenous or exogenous stressors (Larsen, 1997). Viewing these lesions as non-specific indicators of stress and thus not diagnosing the specific cause of periosteal lesions for each individual in a skeletal sample ignores potential variation in morbidity and mortality among those exhibiting the lesions and prevents examination of the relationship between specific diseases and morbidity and mortality (Powell, 1988; Weston, 2012). Nonetheless, the “non-specific” approach can still yield important insights about health and mortality in past populations. For example, previous research has shown that, at least in medieval samples from England and Denmark, periosteal lesions are associated with elevated risks of mortality (DeWitte and Wood, 2008; Usher, 2000). It is important to note that Usher’s study pooled data on both destructive and proliferative periosteal new bone formation lesions for analysis, rather than focusing just on proliferative lesions, so her results are not necessarily directly comparable with other studies that do focus strictly on proliferative lesions. Given that under conditions of both normal (i.e. non-epidemic) medieval mortality and during the 14th-century Black Death, individuals with tibial periosteal lesions were more likely to die than their age peers without these lesions (DeWitte and Wood, 2008), it appears that periosteal lesions can be viewed as a marker of poor health or high frailty (frailty is defined as an individual’s risk of death relative to other members of the population (Vaupel et al., 1979), and individuals with higher frailty are less likely to survive while those with lower frailty are more likely to survive).

In bioarchaeological studies, periosteal lesions are often scored as woven (unremodeled and thus reflecting active disease or inflammatory responses at the time of death) or sclerotic (lamellar or remodeled and thus indicative of healing by the time of death or a chronic disease process) or a combination of the two (Buikstra and Ubelaker, 1994). For the previous studies of the relationship between periosteal lesions and risk of mortality (DeWitte and Wood, 2008; Usher, 2000), data on active, mixed, and healed lesions were pooled for analysis, an approach that is typical in bioarchaeology and often reflects a need to maximize sample sizes for analysis. Thus, what was missing from these studies is an assessment of whether there are survival differentials between individuals who had active periosteal lesions at their time of death and those who had healed lesions, even though there is reason to suspect such a differential might exist.

Several researchers have suggested that the activity (active vs. healed) of skeletal lesions in general (i.e. not just periosteal lesions) might be informative about underlying differences in health or heterogeneity in frailty. For example, (Mays et al., 2002) view remodeled periosteal new bone formation as indicative of individuals who survived longer with disease compared to those with woven bone lesions. Wood et al. (1992) argue that healed skeletal lesions in general might, at least under some circumstances, reflect relatively good health and low frailty as they reflect the survival of a disease process earlier in life (see also the comment by Eisenberg in response to Wood et al.). Based on the distributions of healed vs. active periosteal lesions by age among children below the age of four from a Late Woodland site, Wood et al. suggest that individuals with healed lesions were less likely to die than those with active lesions. Similarly, Novak and Šlaus (2010) found that among subadults from a Roman-period site in Croatia, active periosteal lesions were more frequent among those between the ages of 0–4.9, whereas healed lesions were more common in the 5–14.9 year age group. (Rose, 1985) observed systemic active periosteal lesions (or “infection”) more frequently in subadults compared to adults, and more healed infection in the latter than the former. In medieval Croatian samples, children (between the ages 1 and 11.5 years) with healed periosteal lesions or healed cribra orbitalia had larger dimensions (e.g. diaphyseal lengths adjusted for age) than those with active lesions (Pinhasi et al., 2013). It is possible that both relatively large bone dimensions and healed lesions indicate relatively low underlying frailty. Grauer (1993) reported that healed periosteal lesions and porotic hyperostosis were more common in adults (ages 20–65) in a British medieval sample. Mittler and Van Gerven (1994) discovered in medieval Nubian samples that active cribra orbitalia lesions were limited to infants and children and that older individuals exhibited healing lesions; however, this age pattern might be a reflection of the fact that cribra orbitalia typically only develops during childhood rather than an indication of underlying levels of frailty. Several studies of tooth crown size have reported that juveniles have smaller permanent teeth than adults in the same assemblages (Guagliardo, 1982; Stojanowski et al., 2007). Small crown size can indicate that an individual did not achieve maximum genetic potential because of exposure to developmental stressors, and the smaller size permanent teeth in juveniles suggests higher risks of mortality for those exposed to such stressors (Stojanowski et al., 2007). Relatively large teeth might be considered analogous to absent or healed lesions, given that they can indicate individuals who either avoided developmental stress or survived it and still developed normally despite it. It should be noted that not all previous research has revealed patterns suggestive of survival or health advantages associated with healed skeletal lesions. Shuler (2011), for example, found more healed than active periosteal lesions in adolescents when compared to adults in a 17th–19th-century slave cemetery.

Though several researchers have argued or inferred that healed lesions may indicate lower frailty, to date no study has explicitly and quantitatively tested differences in survival or mortality rates across all ages between those with active versus healed periosteal lesions. Other studies have considered age in the analysis of the *presence* of skeletal stress markers, including but not limited to periosteal lesions (e.g. Cucina et al., 1997; Goodman and Armelagos, 1988; Jankauskas, 2003; Lallo et al., 1978; Novak and Šlaus, 2010; Paine et al., 2007; Pinhasi et al., 2006; Roberts et al., 1998; Steckel et al., 2002; Temple, 2010), but fewer studies have simultaneously examined age patterns and the activity of stress markers. This study builds upon the few previous studies that have examined age patterns of healed and active periosteal lesions by more directly assessing the relationship between periosteal lesion activity and survival. It addresses the question: does the presence of healed or healing periosteal lesions indicate substantial survival advantages in general? Using data from medieval London cemeteries, this study tests the hypothesis that individuals with healed periosteal lesions had higher survivorship compared to those with active lesions.

2. Materials and methods

2.1. Skeletal samples

All skeletal samples ($n = 538$) for this study come from medieval London cemeteries and are curated at the Museum of London Centre for Human Bioarchaeology.

2.1.1. East Smithfield (1349–1350)

The East Smithfield cemetery from east London is one of only a few excavated European cemeteries with both strong documentary and archaeological evidence clearly linking it to the 14th-century Black Death, and it was founded before the arrival of the epidemic for the express purpose of burying victims of the Black Death (Grainger et al., 2008; Hawkins, 1990). Archaeological excavations disinterred over 600 individuals from East Smithfield. Stratigraphic