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Quantitative ultrasonometry for the diagnosis of osteoporosis in human skeletal remains: New methods and standards

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ABSTRACT

Osteoporosis, a complex and heterogeneous disorder with a multi-factorial etiology, is characterized by abnormal bone loss leading to an increased risk of fractures.

In recent years, the study of osteoporosis and bone mineral quality has received increasing interest by biological anthropologists. In particular, the study of bone quality in ancient populations in relation to sex, age and cultural background can provide important insights into the diachronic evolution of a seemingly modern pathology. However, a number of challenges remain in the determination of bone loss in ancient remains, partly due to the methodological approaches applied in the anthropological analysis. This underlines the need for a new methodology and new standards, specifically created and adapted to human skeletal remains.

The current study aims to develop a new methodology to assess bone quality in modern and ancient human skeletal remains using Quantitative Ultrasonometry, applied for the first time to a skeletal sample of known age-at-death and sex (Frassetto collection, University of Bologna). After the assessment of intra- and inter-observer reliability, new ultrasonometric standards based on the analysis of age-related and sex-related changes in bone quantity and quality were created, providing a reference point for the analysis of osteoporosis and bone loss in skeletal remains. The applicability of the method was tested in a medieval sample including both males and females. The low intra- and inter-observer errors suggest that the Phalangeal Ultrasonometry is a reliable and valid technique that can be applied to modern and ancient human skeletons.

1. Introduction

Osteoporosis is a metabolic bone disorder characterized by a compromised bone strength due to low bone density and microarchitectural deterioration of bone tissue, leading to an increasing risk of fracture (Curate, 2014; Dede and Callan, 2018; Golob and Laya, 2015; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). The most common consequences of this condition are three different types of fractures occurring after a moderate trauma, such as a fall: fractures of the proximal femur (hip), vertebral compression fractures, and fractures of the distal junction of the radius (Colles' fracture, Smith fracture) (Curate, 2014; Golob and Laya, 2015; Johnell and Kanis, 2006).

Bone tissue constantly undergoes modeling and remodeling processes throughout life through the action of several types of bone cells (osteoblasts, osteocytes and osteoclasts), whose relative activity determines bone balance (Boyd, 2009; Brickley and Ives, 2008; Curate, 2014; Fleisch, 2000; Golob and Laya, 2015; Gosman and Stout, 2010). During the modeling process, bone tissue is constantly modified in size, shape and position to mechanically adapt bone during the initial skeletal formation; after the end of puberty, remodeling becomes the prevailing metabolic skeletal process (Curate, 2014; Prestwood and Raisz, 2000). Bone tissue is always subject to remodeling processes during the life of the individual in order to respond to new stresses and replace older bone tissue. However, osteoblastic activity decreases with senescence. (Curate, 2014; Gilsanz, 1999; Golob and Laya, 2015; Madimenos, 2015; International Osteoporosis Foundation, 2017). Age-related bone density loss begins after peak bone mass (PBM) and the balance between modeling and remodeling is interrupted, leading to a prevalence of bone resorption over bone formation (Golob and Laya, 2015). Skeletal disorders such as osteopenia (i.e., generalized loss of bone) and osteoporosis occur when excessive osteoclastic activity leads

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to a bone density loss (Curate, 2014; Golob and Laya, 2015).

Osteoporosis is a multiple-etiological disorder influenced by endogenous and exogenous factors, including senescence, sex, hormonal factors, dietary and behavioral habits, genetics, reproductive and lactation factors and physical activity (Brickley and Ives, 2008; Dede and Callan, 2018; Golob and Laya, 2015). Aging is known to be the primary risk factor of osteoporosis, due to decreases in osteoblastic activity and in the intestinal absorption of calcium and other nutrients useful to bone formation (Curate, 2014; Madimenos, 2015; Recker et al., 2004; Riggs and Melton, 1986).

The study of osteoporosis in ancient populations could be helpful to understand the patterns and prevalence of this disease in the past and the present (Agarwal and Grynpas, 1996). Although osteoporosis was first described about 250 years ago (Duverney, 1751), several studies have subsequently underlined how this condition (and a more generalized decline in bone strength) has always affected human groups, especially after the sedentarism following agriculture and domestication (Agarwal et al., 2004; Agarwal and Grynpas, 1996; Beauchesne and Agarwal, 2017; Brickley, 2002; Dewey et al., 1969; Larsen, 2003; Mays, 2016; Ruff et al., 2006, 2015; Ryan and Shaw, 2015; van Gerven et al., 1969). Although it is quite difficult to establish a clear origin of this disease (Curate, 2014; Curate et al., 2013; Mays, 2008), several analytical approaches to the study of ancient evidence of osteoporosis have revealed clear signs of patterns of bone loss. A preliminary diagnosis of osteoporosis in archaeological samples is mainly based on the presence of characteristic fractures in elderly groups of a population, which are usually perceived as osteoporotic, or due to the fragility of the bone structure (Curate, 2014).

In order to apply a more standardized and quantitative methodology in the paleopathological study of osteoporosis, several biomedical techniques have been tested in skeletal samples (Agarwal and Grynpas, 1996; Beauchesne and Agarwal, 2017; Curate, 2014). The most common methods of bone mass evaluation are dual X-ray absorptiometry (DXA) and radiogrammetry. DXA, considered a very accurate method to assess osteoporosis in archaeological skeletal samples (Beauchesne and Agarwal, 2017; Golob and Laya, 2015), calculates the amount of hydroxyapatite in grams of mineral per unit area on a bone through the transition of two radiation stems across the bone; however diagenetic processes can affect the outcomes, and the costs of this method are also quite substantial (Curate, 2014). Radiogrammetry quantifies the amplitude or geometry of the cortical bone in long bones by calculating the ratio between medullary cavity thickness and total width of the diaphysis directly on radiographic images; nevertheless the measurement of the medullary cavity is not always accurate, with a precision of the method around 5–10% (Beauchesne and Agarwal, 2017; Curate, 2014; Ives and Brickley, 2004).

The many studies on osteoporosis in ancient populations highlight the absence of a standardized methodology, a diversified panorama of analytical approaches and several methodological limits often due to age-at-death estimation methods in archaeological samples (Brickley, 2002; Curate, 2014). As pointed out by Curate (2014), the lack of a reference model for ancient populations should be overcome by the creation of a standardized methodology based on a skeletal collection with known age-at-death and sex. Quantitative ultrasonometry (QUS) is based on measurement of the velocity of ultrasound and on interpretation of the characteristics of the ultrasound signal (Wüster et al., 2000). This technique is currently used by clinicians for the assessment of bone mineral status in modern populations (Giavaresi et al., 2004; Hans and Baim, 2017). Phalangeal ultrasonometry applied since 1992, has proved to be a reliable method to diagnose osteoporosis and predict fractures (Baroncelli et al., 2006; Glüer, 1997; Guglielmi et al., 2009; Wüster et al., 2000); based on ultrasound propagation, it provides important information about bone health, such as bone density, bone elasticity and risk of fractures in children, adolescents and adults independently of bone mineral density (Baroncelli et al., 2010; de Terlizzi et al., 2000; Guglielmi et al., 2009). This technique is also useful in assessing properties of bone microstructure, such as elasticity (Barkmann et al., 2000; de Terlizzi et al., 2000; Guglielmi et al., 2009; Wüster et al., 2005), correlated to bone density quality and risk of fractures. The reliability and potential of QUS have also been highlighted in a cadaver study (Wüster et al., 2005), showing how quantitative ultrasound can provide better information than DXA concerning the architecture and mechanical resistance of bone tissue (Wüster et al., 2005). Limitations of the QUS technique are usually associated with the monitoring and correct maintenance of the devices and with the reproducibility of measurements; indeed, precision and reproducibility of measurements are essential for the correct clinical use of QUS devices (Hans and Krieg, 2009; Wuster et al., 1998). Moreover, QUS is most effective when combined with an assessment of clinical risk factors, especially at the start of the monitoring process (Hans and Krieg, 2009).

Therefore, this method provides several advantages, in that it is non-invasive, radiation-free, easy-to use, portable and computer-assisted, and automatically collects a large amount of data (Baroncelli et al., 2006; Guglielmi et al., 2009, 2003; Hans et al., 1998; Wüster et al., 2005, 2000). However, despite its advantages, it has never been applied to skeletal material, as far as we know. The aim of the present study was to develop new quantitative reference standards for the diagnosis of osteoporosis in skeletal human remains by application of Quantitative Ultrasound analyses to phalanges of a large sample of individuals belonging to a modern skeletal collection with known age-at-death and sex (Frassetto collection, University of Bologna). Furthermore, archaeological specimens were used to assess osteoporosis based on comparisons with the new standard curves.

2. Materials and methods

2.1. Osteological samples

Our study included 110 subjects of known sex and age-at-death from the Frassetto collection (Museum of Evolution, Department of Biological, Geological and Environmental Sciences, University of Bologna). These individuals, who died in the early 1900s, were buried in the cemetery of Bologna and their remains were exhumed during the first half of the 20th century to be kept in the museum (Belcastro et al., 2017). In particular, we randomly selected approximately a dozen male subjects and a dozen female subjects for each of the following age groups: 21–30; 31–40; 41–50; 51–60; > 60, until a sample of 100 individuals was reached. Furthermore, ten individuals were randomly chosen from the same collection for cross-validation.

Individuals who died of tuberculosis (cause of death was generally known as well; Appendix A, Supplementary Table 1) were excluded from the analysis due to the well-known destructive effect of this pathology on the bone tissues of several skeletal districts (Choi et al., 2017; Mariotti et al., 2015).

At the end of the experimentation, we applied QUS to a medieval sample of 20 adult subjects from different sites in the Po Valley to exemplify their placement in the new reference curves and the resulting interpretation. These specimens are now part of the osteological collections of the University of Ferrara (Laboratory of Archaeo-Anthropology and Forensic Anthropology, Dep. Biomedical and Specialty Surgical Sciences). Sex and age-at-death of the adult individuals were estimated by traditional anthropological methods (Acsádi and Nemeskéri, 1970; Brooks and Suchey, 1990; Brothwell, 1981; Buikstra and Ubelaker, 1994; Ferembach et al., 1980; Gualdi-Russo, 2007; Lovejoy, 1985; Phenice, 1969; Todd, 1921, 1920). We used the mean age value of each individual (assessed by different methods) to plot the points in the graph of the AD-SoS reference curves, drawing through these points a bar parallel to the x-axis to represent the uncertainty in age determination.