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Osteoporosis and paleopathology: a review

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Summary - *Osteoporosis is a complex and heterogeneous disorder, of multi-factor aetiology. It is the most frequent metabolic bone disorder, affecting an increasing number of post-menopausal women and aging individuals from both sexes. Although first recognized more than 250 years ago, the clinical and epidemiological knowledge about osteoporosis is largely limited to the last 70 years. Within the conceptual frames of paleopathology, disease is necessarily perceived in a space without depth (the skeleton) and of coincidence without development (the crucial moment of death) – but is also interpreted in a time interval which adds an historical gaze to its "biography". The study of osteoporosis in past populations (which faced sociocultural conditions utterly different from the genus vitae experienced by modern communities) supplements diachronic depth to the knowledge about bone modifications related to age, menopausal status or lifestyle. This article aims to provide a comprehensive record on the history of osteoporosis and fragility fractures as perceived by the biomedical, historical and, particularly, paleopathological sciences. As such, the main focus of this review is to present an exhaustive and historical-framed exposition of the studies of osteoporosis, bone loss and associated fractures within the field of paleopathology and, to a lesser extent, in the history of medicine. A biomedical-oriented synopsis of the main operational definitions, etiological agents and epidemiological features of osteoporosis and osteoporotic fractures is also provided*

Keywords - *Osteoporosis, Bone loss, Fractures, History of medicine, Paleopathology.*

Introduction

Osteoporosis (OP) – the «silent thief» – is a metabolic disorder characterized by the reduction in bone mass, impaired bone quality and subsequent increase in the risk of fracture (Consensus Development Conference, 1993; NIH Consensus Development Panel, 2001). The loss of mineral content per unit of volume, alongside trabecular deterioration, concurs to bone fragility and increased propensity to fracture (Strømsøe, 2004). The classical hip, distal radius and vertebral compression fractures are the main clinical complications associated with osteoporosis (Johnell & Kanis, 2006).

Joseph Guichard Duverney (1648-1730), professor of anatomy and surgery at the *Jardin du Roi* (medical school established by Louis XIV of France), first described osteoporosis (without christening it) more than 250 years ago in his posthumous «Traité des Maladies des Os» (Duverney, 1751). In the beginning of the 18th century, Jean-Louis Petit (1674-1750) already had documented the inherent fragility of bones (Petit, 1705). A century later – and after – the readily apparent and recognizable propensity of bones to break due to «fragility» was well acknowledged in the medical literature (e.g., Paiva, 1804; Cooper, 1822). The term «osteoporosis» (from the Greek *ostéon-oûn*: bone, and *póros*: porous) was coined by the French pathologist Johann Lobstein, the Younger (1777-1835), in a text entitled *De l'osteoporose* (Lobstein, 1820). Lobstein characterized it as a disease that causes an increase in the size of bones and a rarefication of their internal tissue. Notwithstanding, the disease described by

Johann Lobstein was probably *osteogenesis imperfecta* (Schapira & Schapira, 1992). A few years later, OP was histologically distinguished from osteomalacia (Pommer, 1885).

Unlike other medical concepts, OP definition has changed substantively, reflecting the state of knowledge about the disease (Schapira & Schapira, 1992; Wylie, 2010). With the inception of clinical radiology, OP was defined as a noticeable loss of bone mass, or as a condition in which bone resorption exceeds bone formation (Nordin, 1987). However, generalized loss of bone should be termed osteopenia (Agarwal, 2008; Frost, 2003). The American endocrinologist Fuller Albright (1900-1969) described osteoporosis as a vertebral fracture syndrome in postmenopausal women, defining it as "too little calcified bone" (Albright *et al.*, 1941). Later, Albright & Riefenstein (1948) proposed two primary categories of osteoporosis: postmenopausal osteoporosis and senile osteoporosis. Riggs & Melton III (1986) refined this scheme with the analogous designations, Types I and II. Although heuristically valuable, the model does not account for the intricate etiopathogenesis of the disease (Marcus & Bouxsein, 2008).

Until the 1990's, different definitions of osteoporosis emerged in the medical literature (Bijlsma *et al.*, 2012). The introduction of dual-energy X-ray absorciometry (DXA) scanners in the late 1980's inspired a raging discussion about the definition of osteoporosis (e.g., Mazess, 1987; Melton III & Wahner, 1989; Nordin, 1987) until the consensus conference promoted by the WHO. In 1992, an experts study group, led by the English clinician and researcher John Kanis, met in Rome and proposed a densitometric definition of osteoporosis: a reduction of bone mineral density (BMD) by 2.5 standard deviations or more from the peak bone mass in early adulthood, taking into account gender and ethnicity (WHO, 1994).

Though it has been suggested since the 19th century that OP is a disease that typically affects older women (Bruns, 1882), it was Albright *et al.* (1941) who first highlighted the role of estrogen depletion in postmenopausal osteoporosis, noticing that vertebral fractures occurred more often in women who were subjected to an early oophorectomy. The relevance of sex steroids in the etiopathogeny of the disease has been comprehensively established by subsequent studies (Almeida, 2010; Lindsay, 2010). However, OP is a complex pathological condition with multiple etiological drives, including senescence, genetics, physical activity, reproductive history, and dietary status (Burnham & Leonard, 2008; Curate *et al.*, 2012; Heaney, 2008; Livshits *et al.*, 2004; Møller *et al.*, 2012; Recker *et al.*, 2004; Zhang *et al.*, 2009).

The demographic profile of the world population changed dramatically in the past few years, with a remarkable increase in the total and relative numbers of elderly individuals. As OP affects a large proportion of the aged population, resulting in fractures that have costly human and economic consequences, it is now recognized as one of the major public health concerns affecting the geriatric community (Becker *et al.*, 2010). Although typically acknowledged as a "modern disease", OP has a vast diachronic depth (Agarwal, 2008; Brickley, 2002; Turner-Walker *et al.*, 2001). The prevalence of the disease has oscillated with the historical changes in its etiological agents, like longevity or nutrition. The study of osteoporosis epidemiology in the past is, therefore, crucial to the scientific perception of the disease. Paleopathology – the study of diseases, human or nonhuman, in the past using a plethora of different sources (Ortner, 2003) – has been focused in age-related bone loss since the late 1960's, with the pivotal papers by Dewey *et al.* (1969) and Armelagos *et al.* (1972), on three Sudanese Nubia samples, and the studies of van Gerven *et al.* (1969) or Perzigian (1973) with prehistoric Native-American materials. The body of knowledge in the paleopathology of osteoporosis has developed since, recounting the long history of bone involution and fragility fractures in past communities all over the world (e.g., Agarwal & Grynpas, 2009; Agnew & Stout, 2012; Curate *et al.*, 2009; Curate *et al.*, 2013b; Lees *et al.*, 1993; Mafart *et al.*, 2008; Mays *et al.*, 1998; Mays *et al.*, 2006; Cho & Stout, 2011; Zaki *et al.*, 2009).

Etiopathogenesis of osteoporosis

Bone tissue constitutes the fundamental template of the skeleton, a complex multifunctional system comprising three key functions: mechanical / structural, protection, and metabolical. Bone is a mineralized connective tissue, composed by an extracellular matrix (organic and inorganic) and a distinctive group of cells (Nolla & Rozadilla, 2004). The organic matrix, which constitutes approximately 25% of the dry bone weight, is largely composed of collagen (Boyd, 2009; Fleisch, 2000; Nolla & Rozadilla, 2004). The inorganic bone phase is formed by hydroxyapatite. Bone cells occur in four fundamental types: osteoblasts, osteoclasts, osteocytes and bone lining cells (Boyd, 2009). Mature bone is macroscopically dissociated in two compartments: trabecular bone, prevalent in the vertebral bodies, pelvis and long bones epiphyses; and cortical bone, which predominates in the diaphysis of the long bones (Fleisch, 2000).

Once formed, bone is exposed to a continuous process of renovation and modification trough modeling and remodeling (Fleisch, 2000; Gosman & Stout, 2010). Bone modeling is a mechanically mediated adaptive process for modifying bone size, shape or position. Bone remodeling is the continuously renewal of bone in the adult skeleton, involving the elimination of mineralized bone by osteoclasts from the surfaces of trabecular and cortical bone. Osteoblasts subsequently lay down new bone matrix that becomes mineralized (Boyce & Xing, 2008; Roberts *et al.*, 2004). Initial skeletal formation depends on the direct apposition of bone but bone remodeling becomes the prevailing skeletal metabolical activity at the end of puberty (Prestwood & Raisz, 2000). Bone remodeling occurs in temporary anatomical structures, first identified by Harold Frost (1969), termed Basic Multicellular Units (BMU). These functional units operate in a cycle of five phases: activation, bone resorption, reversal in the cellular proliferation, bone formation and, at last, bone mineralization (Frost, 2003). Bone remodeling is a dynamic combination of bone formation and resorption. As such, any imbalance in the process favoring bone resorption results in bone loss (Nolla & Rozadilla, 2004).

Almost none of the most common diseases of mankind can be attributed to only one cause; the majority stems from multiple causes, better described as risk factors. In the case of osteoporosis, the risk factors arise at different levels but they are not mutually exclusive (Nordin, 2008). OP is a gargantuan landscape difficult to classify by its pathogenesis: the question remains whether it should be viewed as a unique disease or a group of syndromes of skeletal fragility resulting from a stochastic process (Heaney, 2008; Marcus & Bouxsein, 2008).

Peak bone mass

Peak bone mass (PBM) is defined as the maximum quantity of bone mass acquired during growth (National Osteoporosis Foundation, 2010). Adult bone mass is usually determined by the PBM attained at the third decade of life at which is subtracted the bone mass lost throughout the period of physiological aging (Gilsanz, 1999). Stochastic models by Horsman & Burkinshaw (1989) suggest that two thirds of fracturary risk in women can be predicted on the basis of individual PBM. Peak bone mass is classically influenced by a multiplicity of factors, including genetics (accounting for up to 85% of the variation in bone mass) and ethnical affiliation, sex, nutrition, mechanical loads exerted over the skeleton, parity, and alcohol or tobacco consumption (Burnham & Leonard, 2008; Rizzoli & Bonjour, 2010).

Age

OP prevalence increases with age, fitting a Gompertzian pattern common to other chronic diseases, like atherosclerosis or adenocarcinoma (Melton III, 1990). Age is a risk factor for osteoporosis with direct and indirect effects on bone mass. Osteoblastic activity decreases during the process of senescence; hence, bone formation decelerates (Recker *et al.*, 2004; Riggs & Melton III, 1986). Moreover, intestinal absorption of calcium declines, triggering a state of secondary

hyperparathiroydism and, indirectly, an increase in bone resorption (Halloran & Bikle, 1999; Riggs, 2003). There is also a decrease in the intestinal production of 1,25(OH)2D (vitamin D metabolite) which plays a distinctive role in the etiopathogenesis of osteoporosis. Aging also accounts for the accumulation of damage in osseous tissue and the reduction of viable osteocytes (Vashishth *et al.*, 2003)

Menopause and estrogens

Natural menopause is physiologically defined as the last spontaneous episode of menstrual flow, defined retrospectively a year after (Nelson, 2008). All women experience menopause around the average age of 50 years and age at menopause seems to have remained rather stable trough the last 2000 years (Pavelka & Fedigan, 1991). Fuller Albright first acknowledged estrogen influence on the skeleton in the 1940's but bone regulation mechanisms by estrogens are still poorly documented (Komm *et al.*, 2008). Normal premenopausal levels of estradiol shield the skeleton against the increase of bone turnover. As such, early menopause constitutes a major risk factor for OP. Estrogen depletion is the main cause of postmenopausal bone decline and bone architecture disruption in women, also contributing for age-related bone loss in men (Almeida, 2010; Lindsay, 2010). The decline of estrogen levels increases bone resorption, boosting bone sensitivity to parathyroid hormone (PTH), and reducing the intestinal absorption and renal reabsorption of calcium. Bone formation also decreases (Almeida, 2010; Komm *et al.*, 2008; Nordin, 2008). Estrogen actions are mediated mostly through estrogen receptor α (ERα) and also ERβ. Estrogen induces osteoclast apoptosis, wielding an opposite effect on osteoblasts and osteocytes. The beneficial effects of estrogen are due in part to the ability of estrogen to suppress osteoclastogenic cytokine production in T-cells and osteoblasts (Khosla, 2010).

Genetics and ancestry

Osteoporosis and related phenotypes are highly influenced by genetic factors, which exert significant effects in peak bone mass and age-related bone loss (Williams & Spector, 2007). Bone mineral density is highly heritable, as are other risk factors for osteoporotic fracture, such as proximal femur geometry, bone turnover and bone quality. Most likely, multiple genes mediate susceptibility to osteoporosis, each undertaking a small effect in the osteoporotic phenotypes (Williams & Spector, 2007; Zhang *et al.*, 2009). Several studies have shown an association between candidate genes (e.g., COL1AI, VDR or LRP5) and BMD (Ferrari, 2008). The majority of twin and familial studies suggest that 50 to 80% of BMD variance is genetically determined (Williams & Spector, 2007). BMD and trabecular thickness are probably influenced by genetic differences between ethnical groups (Mitchell *et al.*, 2003). Nevertheless, there is a great variation in the prevalence of osteoporosis and fragility fractures within and among different ethnic groups (Williams & Spector, 2007).

Nutrition

Bone physiology is the result of multiple cellular processes. Obviously, the cells responsible for bone deposition, maintenance or reparation are as dependent of nutrients as any other cell in the body. For example, the production of bone matrix relies on collagen synthesis and modification. The nutrients involved in this process include proteins, vitamins C, D and K, and several minerals. Furthermore, the skeleton stores vast quantities of Ca and P, and the extent of the reserve complies with the daily equilibrium between absorption and excretion of the two elements (Heaney, 2008). Daily Ca requirements are reasonably high, but the absorption efficiency is low and further declines between 40 and 60 years of age, remarkably in women (Fishbein, 2004). When dietary calcium absorption is insufficient to counteract urinary and fecal losses, calcium is resorbed from the skeleton – which contains 99% of the body's calcium stores – to uphold serum Ca at a stable level (National Osteoporosis Foundation, 2010). Protein intake is probably related with calcium phosphate metabolism, bone mass and even osteoporotic fracture risk, but any

enduring impact of dietary protein on bone mineral metabolism and bone mass so far has been problematic to detect (Rizzoli & Bonjour, 2010). Alcohol and coffee consumption probably influence bone metabolism but their effect on bone mass is contentious (Nordin, 2008).

Physical activity

Skeletal response to physical activity is seemingly mediated by genetic and hormonal factors (Uusi-Rasi *et al.*, 2008). In accordance with Carter (1984), the mechanical forces applied to the bone stimulate both osteoclastic and osteoblastic activity. Physical activity during growth, especially strenuous activities, excite osteogenic processes influencing peak bone mass (Burnham & Leonard, 2008). Physical exercise also benefits bone health in postmenopausal women and aging individuals from both sexes (Kaptoge *et al.*, 2003). The impact of the loading external environment on bone structure and biology is termed mechanobiology (Gosman & Stout, 2010). Julius Wolff (1892) recognized that the structural and geometrical properties of the bone could be described under a general principle, Wollf's law, in which healthy bone adapts to the loads that impact it. Also, Wilhelm Roux suggested that functional adaptation of trabecular bone is autoregulated and that bone cells respond to local mechanical stimuli (Gosman & Stout, 2010). Drawing on Roux's theory, Harold Frost proposed that bone architecture is under the control of a biomechanical cybernetic system, the mechanostat (Frost, 2003). This system directs bone modeling, and as a result, directs its spatial organization, load capacity and force translation proficiency. The pressure wielded by external interference factors, like physical activity, triggers a feedback control loop and bone adapts its biomechanical properties according to the mechanical function, i.e., bone mass, bone geometry and consequently bone strength.

Reproductive factors

During gestation and breastfeeding, substantial changes take place in the maternal bone mineral metabolism and calcium homeostasis to fulfill the calcium requirements of the fetus and the neonate (Møller *et al.*, 2012). The maternal skeleton strives to adjust to the demand of Ca and other minerals throughout pregnancy (especially during the last trimester), which are relocated through the placenta to mineralize the developing fetal skeleton. Similarly, the increasing needs of calcium during breastfeeding also press for an adjustment of the bone mineral homeostasis in the lactating women (Agarwal, 2008; Møller *et al.*, 2012). Although bone mineral density declines during pregnancy and breastfeeding, the decline is transient (Karlsson *et al.*, 2005; Møller *et al.*, 2012) and BMD can be maintained in a context of increased reproductive stress (Henderson *et al.*, 2000). Later in life, parity (number of births) appears to protect bone health (Streeten *et al.*, 2005). Early age at menarche (first menstrual cycle) is also related with higher bone mineral density (Ito *et al.*, 1995).

Secondary osteoporosis

Secondary osteoporosis is more common in males, stirring fractures at an earlier age. The development of secondary OP is influenced by several factors, including prolonged immobility, hypogonadism, inadequate nutrition, and a panoply of pathological conditions (Nolla & Rozadilla, 2004; Painter *et al.*, 2006).

Osteoporosis in paleopathology

Bone loss in the past

Although described during the 18th century (Duverney, 1751), clinical awareness about osteoporosis was essentially nonexistent before the mid-19th century. As such, paleopathological investigations of osteoporosis and its sequels (the fractures) can provide a relevant insight into the diachronic evolution of a seemingly modern nosological entity. Thus, the studies of the galaxy of osteoporosis in the past developed noticeably in the last decades, with additional and important references of cultural and social experiences from past lives.

Even though paleopathological studies do not reveal uniform patterns of bone loss in the past, a growing body of osteological data proves beyond doubt that OP has occurred throughout human history (Agarwal & Grynpas, 1996; Agarwal, 2008; Brickley & Ives, 2008). A report by Dewey and colleagues (1969) probably features the first advance of paleopathology into the vast landscape of osteoporosis. The study was of major importance since it established osteoporotic bone loss as an age-related degenerative process with historical depth. The analysis included skeletal Nubian samples from the Meroitic (350 BC – 350 AD), X-Group (350 – 550 AD) and Christian (550 – 1400 AD) periods. The authors were able to demonstrate a significant decrease in the femoral cortical thickness with age in Nubian women. Also, the loss of cortical bone in Nubian females appears to have begun earlier than in modern counterparts. In the same year, van Gerven *et al.* (1969) studied femoral cortical bone in a sample of prehistoric Mississipians (1540 – 1700 AD), suggesting that the reduction in cortical thickness with age (in both sexes) was comparable with the loss in modern populations. The authors also found that the cortical bone decline occurred earlier and was steeper in females.

Early paleopathological studies documented a similar pattern of bone loss in different past communities, with age-related bone loss and greater loss in females (Carlson *et al.*, 1976; Ericksen, 1976; Laughlin *et al.*, 1979; Martin & Armelagos, 1979; Martin *et al.*, 1985; Ruff & Hayes, 1982; Thompson & Guness-Hey, 1981). Some of the more recent studies have also found age-related bone loss in past populations, remarkably pungent in post-menopausal women, suggesting that the general patterns and prevalence of osteoporosis were essentially the same as in modern populations (Cho & Stout, 2011; Curate *et al.*, 2009; Curate *et al.*, 2013b; Fulpin *et al.*, 2001; Glencross & Agarwal, 2011; Hammerl *et al.*, 1990; Kneissel *et al.*, 1997; Mafart *et al.*, 2002; Mafart *et al.*, 2008; Mays, 1996; Mays *et al.*, 1998; McEwan *et al.*, 2004; Zaki *et al.*, 2009). Nonetheless, other studies have found different patterns of bone loss – unlike those of modern westernized populations – with less bone loss than modern populations (Drusini *et al.*, 2002; Lees *et al.*, 1993; Mays, 2000; Mays, 2001; Rewekant, 1994), trivial or no loss with age in one or both sexes (Agarwal *et al.*, 2004; Brickley & Waldron, 1998; Ekenman *et al.*, 1997; Lynnerup & von Wowern, 1997; Poulsen *et al.*, 2001), precocious bone loss in females (Armelagos *et al.*, 1972; Holck, 2007; Mays, 2006a; Mays *et al.*, 2006; Poulsen *et al.*, 2001; Rewekant, 2001), and/or irrelevant differences between sexes (Beauchesne & Agarwal, 2011).

Chronological and geographical differences in risk factors, like genetics, ages at menarche and menopause, physical activity, reproductive status or diet, certainly accounted, at least partially, for the different patterns observed It is unclear whether these distinct bone loss patterns are also due to the nature of mortality sample demographics such as the heterogeneity of older age groups, methodological difficulties with age at death determination and sex diagnosis, bone loss in young-age women reflecting transient reproductive stress, or differing bone loss assessment methods and skeletal sites of analysis (Agarwal, 2008; Agarwal & Grynpas, 1996; Brickley & Agarwal, 2003). As an example, physical exercise shows a differential effect on cortical and trabecular bone density, increasing the latter while leaving the former mostly unaltered (Hagihara *et al.*, 2009).

Since the papers by Dewey *et al.* (1969) and van Gerven *et al.* (1969), several paleopathological studies have focused on the association between bone mass and nutrition (Agarwal, 2008; Brickley & Ives, 2008). The apparent poorer nutrition of some past populations probably played a role in the acquisition of bone during growth (Mays, 2008b), influencing peak bone mass and bone mass later in life (Rizzoli & Bonjour, 2010). Calcium intake has been extensively discussed in the anthropological literature, although recent clinical and epidemiological studies have raised doubts over the effects of calcium on bone loss (Agarwal, 2008). Nutritional change during the Neolithic

Revolution is associated with lower bone mass in the first agricultural populations (Nelson *et al.*, 2002) – a substantial modification in the sources and quantities of Ca certainly occurred during the transition to agriculture (Agarwal, 2008; Brickley & Ives, 2008; Smith *et al.*, 1984).

The data obtained in the Nubian samples have been classically interpreted as a reflex of chronic malnutrition (Armelagos *et al.*, 1972; Dewey *et al.*, 1969). Nutritional stress has also been related with bone loss in several Native-American and Arctic communities (Cassidy, 1984; Ericksen, 1976; Ericksen, 1980; Nelson, 1984; Pfeiffer & King, 1983; Richman *et al.*, 1979; Thompson & Gunness-Hey, 1981). Ericksen (1980) linked the high-protein diet of the Eskimo and the low-protein diet of the Arikara to the differences in the bone remodeling parameters of both groups. Protein intake probably influences calcium phosphate metabolism and bone mass but clinical research failed to observe any long-term impact of dietary protein on bone metabolism (Rizzoli & Bonjour, 2010). *Contra mundum*, Anthony Perzigian (1973) suggested that dietary sufficiency did not contribute substantially to the maintenance of both cortical and trabecular bone during aging in two prehistoric Native-American populations. More recently, the high prevalence of osteopenia in prehistoric collective burials from Gran Canaria (Spain) was justified by episodes of food shortage and dietetic deficits (González-Reimers *et al.*, 1998; González-Reimers *et al.*, 2007). Notwithstanding, the estimation of age at death could not be accomplished (and, sometimes, also sex diagnosis) in most of the samples; as such, any interpretation that links nutrition with bone loss in these populations is seriously flawed (Agarwal, 2008).

Another research pathway has emphasized the importance of mechanical loading and physical activity in the maintenance of bone mass and structure (Lees *et al.*, 1993; Mulhern & van Gerven, 1997; Peck & Stout, 2007; Pfeiffer & Lazenby, 1994). The increased physical loading impacts both bone geometry (distribution) and mass (Hagihara *et al.*, 2009). During the Neolithic revolution, the subsistence shift was accompanied by an increase in sedentarism. Some indicators of activity seemingly suggest a decline in workload with the adoption of agriculture. As a rule, bone geometry parameters also reveal a decline in bone strength associated with increased sedentarism following agriculture and animal domestication (Larsen, 2003; Ruff *et al.*, 2006). The archaeological data indicates that the overall decline in physical activity can be a contributing factor to the rise in the incidence of osteoporosis in modern populations (Lees *et al.*, 1993). It is important to remind that workload was very flexible in hunter-gatherers and horticulturalist groups, and also in more recent populations (Larsen, 2003). Also, other factors beyond physical activity influence the structural behavior of bones, including age, sex and disease (Cole & van der Meulen, 2010).

Ruff *et al.* (1984) evaluated changes in femoral cross-sectional geometry in a diachronic Native-American sample (Pecos Pueblo) comprising both hunter-gatherer and horticulturalist groups. The authors observed a decline in cross-sectional area, which resulted from a decrease in mechanical loading following a reduction of activity levels and an increase of sedentarism with the adoption of agriculture. Although bone mass declines with age, Ruff & Hayes (1983) found that the matching increase in external dimensions caused by continuing subperiosteal expansion offsets biomechanically the loss of bone, resulting in the maintenance of bone strength in the elderly individuals from Pecos Pueblo. The role of mechanical loading in bone health is deeply discussed in several paleopathological populations, but it is obvious that the effects of physical activity cannot be interpreted secluded from other factors, like nutrition (Agarwal, 2008; Pfeiffer & Lazenby, 1994). For example, Ericksen (1980) examined the patterns of bone loss in three Native-American and Arctic populations and suggested that the differences observed were due to dietary and physical activity differences between the groups. Finally, variation in the size of structures within mature cortical bone, like osteons, does not appear to be connected to physical activity (Pfeiffer *et al.*, 2006).

Reproductive factors have also been pondered in the explanation of bone loss in historical populations, particularly in females. Bone mass related to reproductive behavior has been considered in several archeological populations, with decreased bone mass in young adult females interpreted as the result of temporary reproductive stress (Agarwal, 2008; Agarwal & Stuart-Macadam, 2003; Brickley & Ives, 2008). Dewey *et al.* (1969) detected precocious cortical thinning in Nubian females, caused by a combination of poor calcium intake and extended breastfeeding. Armelagos *et al.* (1972) also proposed that the early cortical bone loss observed in Nubian women echoes the physiological stress connected to prolonged breastfeeding and deficient calcium consumption. Likewise, other authors have suggested that bone loss in young adult females from European medieval samples could be related to the hazards of pregnancy and breastfeeding (Agarwal *et al.*, 2004; Mays *et al.*, 2006; Poulsen *et al.*, 2001; Turner-Walker *et al.*, 2001). On the contrary, a radiogrammetric study in a young females' sample from pre-industrial Coimbra Identified Skeletal Collection did not found significant differences in the cortical parameters of the second metacarpal between those that died during or shortly after birth («maternal deaths») and those that died from other causes (Curate *et al.*, 2012). Most epidemiological studies have found that bone mineral density decreases during pregnancy and breastfeeding, resuming shortly after weaning. Nevertheless, BMD can be preserved in a setting of increased reproductive stress. Parity also appears to have a protective effect on bone mass later in life (Henderson *et al.*, 2000; Karlsson *et al.*, 2005; Møller *et al.*, 2012; Streeten *et al.*, 2005). The relationship between reproductive factors and bone loss is, at best, inconsistent and bone mass during pregnancy and breastfeeding is also influenced by diet, physical activity or body weight (Karlsson *et al.*, 2005; To & Wong, 2012).

The numerous studies of bone loss in historical populations have relied on diverse analytical approaches, without the standardization of investigation methodologies, enfeebling the classical anthropological comparative research (Agarwal, 2008; Brickley & Ives, 2008). Nonetheless, several archaeological samples clearly show patterns of bone loss that emulate those of modern, westernized, populations – far from being a «disease of civilization», osteoporosis apparently has a history with deep roots in the past (Curate *et al.*, 2013b; Mays, 2008b). Evidently, the etiology of bone loss in historical populations can never be conclusively established – the causes of bone loss and OP are multiple, not unequivocal or undisputed – but the primary causes of osteoporosis in modern populations, such as estrogen withdrawal, nutrition or senescence, were already affecting bone health in the past. While some paleopathological studies have insisted in allocating definite causes for bone loss in the past, like diet or physical activity, others emphasized complex and holistic approaches (Agarwal, 2008). The latter research approach, which integrates anthropological and clinical knowledge about bone loss, is certainly the superlative way to gain diachronic insight about osteoporosis.

Osteoporotic fractures in the past

Osteoporosis can be crippling but is 'silent' (symptomless) prior to bone fracture (Wylie, 2010). The term fracture designates a complete or partial break in the continuity of a bone (Müller, 1990). The general fracture pattern in the population has peaks in the younger and elderly groups. The fractures affecting the latter group are usually perceived as osteoporotic or fragility fractures, and they are often related with moderate trauma at trabecular-rich skeletal sites. Their incidence increases with age, being higher in females (Strømsøe, 2004). Fragility fractures are commonly associated with a fall to the floor from an orthostatic position (Kannus *et al.*, 1996). Low BMD is related with an increased fracturary risk at the population level (Strømsøe, 2004). The spatial distribution of bone (i.e., bone geometry), bone quality and propensity for falling also stand as chief risk factors for fragility fractures in the elderly (Pietschmann *et al.*, 2009). Osteoporotic fractures typically occur in the vertebral body, the distal radius and the proximal

femur (Johnell & Kanis, 2006). Likewise, fractures of the proximal humerus (Fig. 1) are often related to an osteoporotic disorder (Reitman *et al.*, 2008).

The anatomical relevance and the social and cultural repercussions of trauma in past communities are categorical (Lovell, 1997) and a multiplicity of publications have made consequential contributions to the way in which trauma has been used to recognize and interpret accidental injury or interpersonal violence throughout history (e.g., Domett & Tayles, 2006; Djurić *et al.*, 2006; Mitchell, 2006). Although ubiquitous in the archeological record, fractures are, most of the times, related to traumatic events and not with bone intrinsic frailty (Dequeker *et al.*, 1997). Fragility fractures – especially fractures of the proximal femur – were deemed infrequent in archaeological samples (Agarwal *et al.*, 2004; Brickley, 2002; Ortner, 2003) but evidences of osteoporotic fractures in the past are growing steadily (Curate *et al.*, 2011).

The assumed low frequency of fragility fractures in the past is commonly explained as the result of selective mortality and low life expectancy at birth in historical populations. As such, the lower prevalence of these fractures in archeological skeletal samples suggests that the older cohorts in the past were resilient to the action of natural selection, being genetically more adapted to adverse environmental circumstances (Agarwal *et al.*, 2004; Agarwal, 2008). One of the themes of the well-known osteological paradox (Wood *et al.*, 1992) conveys the notion that individuals differ considerably in the susceptibility to illness, and that the factors that subsidize this discrepancy are usually not identifiable – while genetics can surely prompt frailty; other factors will also be involved in the predisposition for disease (Wright & Yoder, 2003). In short, any unidimensional hypothesis on the causes of OP and associated fractures tends to overlook the hybrid nature of the human body, simultaneously biological and cultural (Sofaer, 2004).

Also, the notion that few individuals reached a sufficiently advanced age to sustain an osteoporotic fracture is somewhat flawed. The low life expectancy at birth in the past is closely connected to an exceptionally high infant mortality, and the individuals that surpassed the critical stage of infancy had good chances of living into old age, being more prone to chronic diseases, like OP and attendant sequels (Brickley & Ives, 2008). Also, paleodemographic profiles are more influenced by fertility than mortality (Wright & Yoder, 2003), which does have major implications in the absolute and relative number of old adults in any given sample.

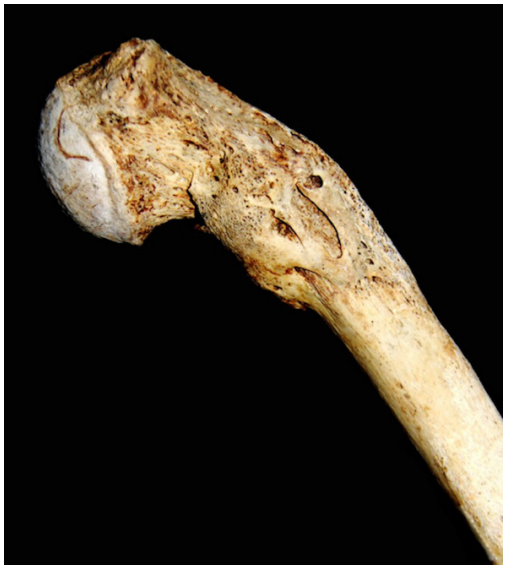

Fig. 1 - Fracture of the cirurgical neck of the left humerus, with pronounced angulation and bone repair; male, 83 years (Identified Skeletal Collection of Coimbra). The colour version of this figure is available at the JASs website.

Factors beyond bone mass, like bone quality and geometry, environmental hazards or propensity to falls, can explain the low prevalence of fragility fractures in most past populations (Agarwal & Grynpas, 1996; Agarwal *et al.*, 2004; Mays, 2008b) – but fracture patterns can only be fully perceived within a biocultural, context-specific, framework. In fact, the prevalence of osteoporotic fractures in past communities seems to display geographical and chronological variations instead of uniform patterns of low frequency. This should

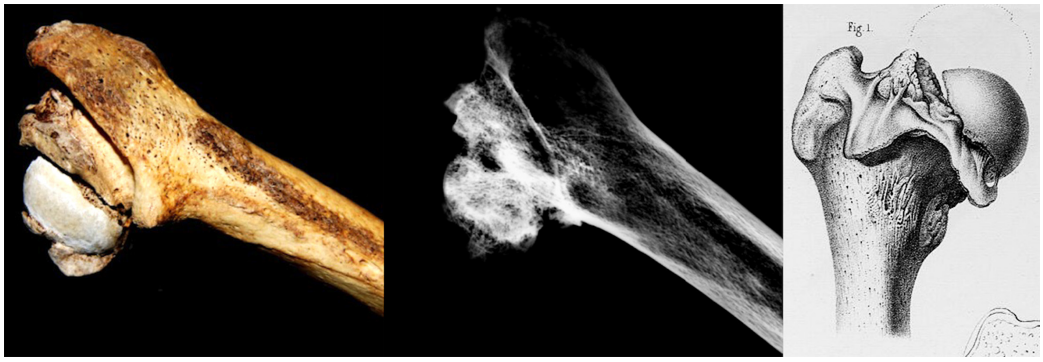

Fig. 2 - Intracapsular fracture with varus deformity of the head of femur (possibly a sub-capital fracture); female, 80 years (Identified Skeletal Collection of Coimbra). Notice the similarity with a case depicted in Malgaigne (1847: plate XI). The colour version of this figure is available at the JASs website.

be at least considered since nowadays the severity and frequency of osteoporosis and related fractures varies considerably among different populations (Johnell & Kanis, 2006). To maintain that osteoporotic fractures «in the past» were not frequent is an essentializing statement that embraces a view of historical populations as uniform and archetypal entities (Sofaer, 2004).

The comparison of osteoporotic fractures' frequency between archeological and living samples is constrained by the nature of the epidemiological data (usually presented as incidence rates) versus the paleoepidemiological data (only the prevalence rates can be calculated). As such, similarities or dissimilarities in fracture frequency between skeletal and in vivo populations are restricted to those few studies that tabulate fracture prevalence according to age and sex classes (e.g., Kwok *et al.*, 2013; van der Voort *et al.*, 2001).

Alternatively, only the general pattern of fracture occurrence should be compared. The study of fractures in skeletal assemblages from archeological sites is also limited by poor bone preservation, unsatisfactory age at death estimation in adults and disparate scoring methods (Judd & Roberts, 1998). Moreover, older individuals are more likely to present bone fractures simply because they lived longer and the probability that they sustained a fracture is higher (Glencross & Sawchuk, 2003; Mays, 2008b). Finally, most of the times it is impossible to establish the exact individual age at which the fracture occurred (Domett & Tayles, 2006).

A small fraction of paleopathological studies on fractures have addressed the association of bone mass with fragility fractures (Curate *et al.*, 2009; Curate *et al.*, 2013b; Foldes *et al.*, 1995; Frigo & Lang, 1995; Kilgore *et al.*, 1997; Mays, 2000; Strouhal *et al.*, 2003; Mays, 2006a, Mays *et al.*, 2006b; Domett & Tayles, 2006). In these studies, osteoporotic fractures are usually correlated with low bone mass. For example, Curate *et al.* (2013b) found that women with osteoporosis had a much higher probability of showing a fragility fracture than women of the same age diagnosed with normal or osteopenic values of BMD. There is a possibility that bone loss occurred *after* fracture and not *before* (Brickley & Ives, 2008) but evidences that non-fragility fractures are not associated with low bone mass argue against that hypothesis (Mays *et al.*, 2006).

Fractures of the proximal femur, or hip fractures, were clinically acknowledged in the 16th century by the French surgeon Ambroise Paré (1575). Hip fractures, defined as those taking place above a 5 cm point underneath the distal portion of the lesser trochanter until the femoral head, are classically categorized according the anatomical location. Intracapsular fractures (also cervical or femoral neck fractures) occur inside the hip joint capsule, above the trochanters (Fig. 2); and extracapsular fractures (also trochanteric or

Fig. 3 - Subtrochanteric fracture of the right femur (individual of unknown provenance and chronology, Museum of Anthropology of the University of Coimbra). The colour version of this figure is available at the JASs website.

pertrochanteric fractures; Fig. 3, previously unreported) occur distally from the hip joint capsule (Nolla & Rozadilla, 2004). Hip fractures are frequently an outcome of bone loss and augmented risk of falling among the elderly, affecting aged individuals from both sexes, but predominantly older women (Cauley *et al.*, 2008).

A growing body of paleopathological studies suggests that hip fractures were, if not moderately common, at least present in past populations (Tabs. 1 and 2) (e.g., Bartonícek & Vlcek, 2001; Buzon & Richman, 2007; Curate *et al.*, 2010; Curate, 2011; Curate *et al.*, 2011; Dequeker *et al.*, 1997; Ferreira & Silva, 2002; Garcia, 2007; Ibáñez, 2001; Ives, 2007; Kilgore *et al.*, 1997; Lovejoy & Heiple, 1981; Mays, 2006a; Mensforth & Latimer, 1989; Roberts & Manchester, 1995; Stroud & Kemp, 1993). The extensive bone remodelling associated with several of the reported fractures implies some sort of social assistance and care to the affected individuals, at least during recovery, which promoted their survival to a life threatening and disabling event (Brickley, 2002; Curate *et al.*, 2010; Curate *et al.*, 2011). These reports add further information to the clinical texts dedicated to hip fractures produced since the sixteenth century (e.g., Paré, 1575; Ludwig, 1755; Lourenço, 1761; Cooper, 1822; Malgaigne, 1842). Factors beyond bone mass, such as bone quality, falling patterns, stature or proximal femur geometry, may account for the lower frequency of hip fractures in the past (Grynpas, 2003; Navega *et al.*, 2013; Sievänen *et al.*, 2007).

Distal radius fractures cover all fractures of the distal and metaphyseal areas of the radius. A Colles' fracture most commonly involves the distal cortico-cancellous junction of the radius, with dorsal tilt and other displacements. A Smith fracture (or reverse Colles' fracture) is ventrally angulated, with the hand and wrist displaced volarly with respect to the forearm. These fractures usually result from a fall upon an outstretched hand (Mays, 2006b; Nolla & Rozadilla, 2004). Colles' fracture obviously bear the name of the Irish surgeon Abraham Colles, who thoroughly described it in 1812. Notwithstanding, it was the French surgeon Claude Pouteau who first documented this lesion in the distal radius (Pouteau, 1783). Distal radius fractures exhibit a bimodal distribution, occurring in infancy/adolescence and in old age. Colles' fracture incidence increases hastily after menopause, reaching a plateau in the mid-sixties (Nolla & Rozadilla, 2004). Changes in the risk of falling interact with osteoporosis

Tab. 1 - True prevalence of hip fractures in skeletal samples.

SOURCE	SITE	CHRONOLOGICAL PERIOD	N	WITH FRACTURE	%
Kilgore *et al.* (1997)	Kulubnarti, Nubia	Medieval	281	1	0,4
Ives (2007)	Several sites, UK	Post-Medieval	1180	7	0,6
Garcia (2007)	Leiria, Portugal	12th-16th AD	46	1	2,2
Curate *et al.* (2010)	Santa Clara, Portugal	14th-17th AD	66	1	1,5
Curate *et al.* (2011)	São Julião, Portugal	14th-19th AD	43	1	2,3
Curate *et al.* (2011)	Sr.ª da Conceição, Portugal	18th-19th AD	14	1	7,1
Curate *et al.* (2011)	Paimogo I, Portugal	Late Neolithic	78	1	1,3

Tab. 2 - Total prevalence of hip fractures in skeletal samples.

SOURCE	SITE	CHRONOLOGICAL PERIOD	N	WITH FRACTURE	%
Mensforth and Latimer (1989)	Hamann-Todd, USA	19th-20th AD	938	23	2,5
Mays (2006)	Ancaster, UK	3rd-4th AD	39	1	2,6
Curate *et al.* (2010)	Santa Clara, Portugal	14th-17th AD	71	1	1,4
Curate *et al.* (2011)	São Julião, Portugal	14th-19th AD	106	1	0,9
Curate *et al.* (2011)	Sr.ª da Conceição, Portugal	18th-19th AD	30	1	3,3
Curate *et al.* (2011)	São Francisco, Portugal	14th-17th AD	103	1	1,0
Curate *et al.* (2011)	Paradela, Portugal	12th-19th AD	100	1	1,0

Tab. 3 - Prevalence of Colles' fractures in archaeological samples.

SOURCE	SITE	CHRONOLOGICAL PERIOD	N	WITH FRACTURE	%
Redfern (2010)	Dorset, UK	Iron Age	---	1 (♂)	1,9
Redfern (2010)	Dorset, UK	Iron Age	---	1 (♀)	2,1
Redfern (2010)	Dorset, UK	1st-4th AD	---	1 (♀)	2,4
Garcia (2007)	Leiria, Portugal	12th-16th AD	87	3	3,4
Kilgore *et al.* (1997)	Kulubnarti, Nubia	Medieval	259	13	5,0
Domett & Tayles (2006)	Prehistoric Thailand	2000-400 BC	48	1	2,1
Mays, 2006a	Ancaster, UK	3rd-4th AD	39	4	10,3

and are partially accountable for the perimenopausal increase in the incidence of distal radius fractures (Winner *et al.*, 1989).

Colles' fractures are fairly common in the paleopathological literature (e.g., Anderson *et al.*, 1993; Brothwell & Browne, 1994; Curate, 2001; Domett & Tayles, 2006; Duhig, 1999; Garcia, 2007; Grauer and Roberts, 1996; Ives, 2007; Kilgore *et al.*, 1997; Lovejoy and Heiple, 1981; Mafart *et al.*, 2002; Mays, 1991; Mays, 2006b;

Miles, 1989; Redfern, 2010; Reis *et al.*, 2003; Roberts & Wakely, 1992; Stroud & Kemp, 1993; Wells, 1982) and although their prevalence is generally low (Tab. 3), it is not lower than other types of fracture (e.g., Garcia, 2007; Redfern, 2010). Medical authors, like Astley Paston Cooper (1822) or Guillaume Dupuytren (1847), suggested that distal radius' fractures were very common in the first quarter of the 19th century. For example, during the 1829/1830 biennium, Dupuytren recorded 45 (out of a total of 206 fractures) fractures of the distal radius in the Hotel de Dîeu, Paris. This frequency is similar to the prevalence observed in modern Trauma and Orthopedic Services (Nolla & Rozadilla, 2004). Morbidity associated to Colles' fractures is reduced but, occasionally, some residual deficit in the affected forearm persists over time. One paleopathological study suggested that distal radius fractures seldom healed without deformity (Grauer & Roberts, 1996).

Vertebral compression fractures are the hallmark of the «silent thief», being the most prevalent fracture in postmenopausal women (Johnell & Kanis, 2006; Nolla & Rozadilla, 2004). Notwithstanding, vertebral fractures are inadequately defined (there is not a consensual definition) and frequently asymptomatic, which induces an underestimation of their true incidence in the clinical practice (Grados *et al.*, 2009).

Paleopathological descriptions of vertebral compression fractures are common but they usually refer to anecdotal cases (e.g., Foldes *et al.*, 1995; Ortner, 2003; Reis *et al.*, 2003; Sambrook *et al.*, 1988; Strouhal *et al.*, 2003) or to poorly defined methods for the identification of vertebral fractures (e.g., Domett & Tayles, 2006; Hirata & Morimoto, 1994; Ives, 2007; Mays, 1996, 2006a; Mays *et al.*, 2006; Mensforth & Latimer, 1989; Snow, 1948). The «Spine Score» (Barnett & Nordin, 1960) has been used for the assessment of vertebral fractures in archaeological samples (González-Reimers *et al.*, 2004). In a small number of paleopathological studies (e.g., Curate *et al.*, 2009; Garcia, 2007), Genant's semi-quantitative method (Genant *et al.*, 1993) was applied for the assessment of vertebral fractures. The «International Society for Clinical Densitometry» endorses Genant's method to diagnose vertebral fractures in the clinical setting (Schousboe *et al.*, 2008). The method is easy to apply, successful in ruling out vertebral deformities due

Fig. 4 - «Arrival of the English Ambassadors» (detail), Vittore Carpaccio, 1495-1500, tempera on canvas (Gallerie dell'Accademia, Venice). The old woman on the footstep of the stairway most likely suffered from spinal osteoporosis (Dequeker, 1994). The colour version of this figure is available at the JASs website.

Fig. 5 - «El Chiton», Francisco Goya 1764-1824, aquatint (private collection). The old humpbacked woman with the walking stick exhibits some features that probably correspond to a diagnosis of spinal osteoporosis (Curate & Tavares, 2011). The colour version of this figure is available at the JASs website.

to causes other than low bone mass, and highly reproducible. As such, should be applied to score vertebral fractures/deformations in paleopathological studies. Spinal osteoporosis has also been suggested in paintings from Vittore Carpaccio (Fig. 4) (Dequeker, 1994), Piero della Francesca (D'Antoni & Terzulli, 2008) and Francisco Goya (Fig. 5) (Curate & Tavares, 2011).

Diagnosis of osteoporosis in paleopathology

Bone loss in historical skeletal remains can be investigated via a comprehensive number of methods, which offer different – and not necessarily conflicting – views of bone remodeling and maintenance (Brickley & Agarwal, 2003). Unfortunately, results obtained with different methodologies are not directly compared Moreover, some of the methods used in clinical context cannot be applied in paleopathological studies, due to the nature of the investigation object (after all, the ontological chasm between a dead and a living body is striking), to the confounding effects of diagenesis, and to the absence of operational definitions (Agarwal & Grynpas, 1996; Brickley & Agarwal, 2003; Curate *et al.*, 2009).

Bone mass evaluation techniques in archeological skeletal samples display a substantial range of variability with relation to relevance, accuracy, repeatability, technical difficulty, availability and cost (Brickley & Agarwal, 2003; Curate *et al.*, 2009). There is no such thing as a perfect or faultless technical procedure for bone mass assessment but, undoubtedly, some techniques are better than others – and even more so in archeological contexts. Dual x-ray absorptiometry and radiogrammetry are probably the most used techniques to study bone loss in past populations (Mays, 2008b). As such, they are described more comprehensively. Other technical procedures are briefly depicted. For extensive reviews of the methods used to assess osteoporosis and bone loss in paleopathology see Agarwal & Grynpas (1996), Brickley & Agarwal (2003), Curate (2005) and Mays (2008a).

Dual X-ray absorptiometry (DXA)

Osteodensitometry, or DXA, embodies the archetypal bone mass assessment methodology. There is a broad consensus regarding the prominence of DXA in predicting the risk of fracture at the population level (Bonnick, 2010). Also, absorptiometric methods, such as DXA, provide an accurate diagnosis of osteoporosis in skeletal samples coming from archaeological contexts (Agarwal, 2008; Mays, 2008a). DXA calculates the amount of hydroxyapatite in bone, expressing it in grams of mineral per area unit (Fig. 6). The technology involves radiation that stems from two discrete sources: low energy beams are attenuated more steeply than the high-energy beams, and the attenuation is greater in bone.

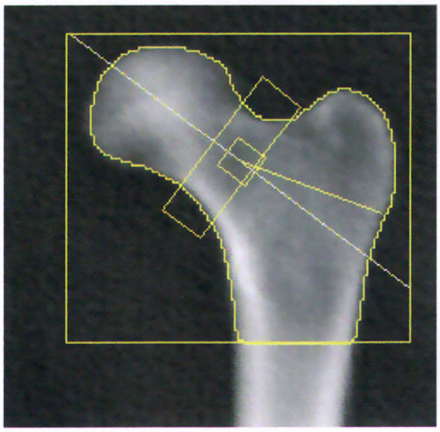

Image not for diagnostic use
k = 1.162, d0 = 61.6
101 x 91
NECK: -49 x 15

Scan Information:

Scan Date: 23 May 2013 ID: K0523131R
Scan Type: a Left Hip
Analysis: 23 May 2013 17:39 Version 12.6:5
Left Hip
Operator:
Model: QDR 4500C (S/N 47998)
Comment:

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
Neck	4.61	2.87	0.622	-2.0	73	-0.8	87
Troch	10.15	5.18	0.510	-1.9	73	-1.1	82
Inter	17.34	14.83	0.855	-1.6	78	-1.0	85
Total	**32.11**	**22.88**	**0.712**	**-1.9**	**76**	**-1.0**	**85**
Ward's	1.11	0.50	0.448	-2.4	61	-0.6	87

Total BMD CV 1.0%, ACF = 1.023, BCF = 1.011, TH = 1.136
WHO Classification: Osteopenia
Fracture Risk: Increased

Fig. 6 - DXA report in a 58-year-old woman from the Coimbra Identified Skeletal Collection, performed in the left femur. Basic results and the WHO classification for this individual are presented. The colour version of this figure is available at the JASs website.

The radiation source is collimated into a «pencil beam» and pointed to a radiation detector positioned away from the place of measurement. The bone mineral content (BMC) affects the attenuation of the radioactive beam. The bone area is determined by specific software and bone mineral density is calculated as the ratio of measured mineral content per area (Bonnick, 2010). DXA does not measure bone volumetric density and BMD results are not entirely standardized for bone size (Bonick, 2010; Lees *et al.*, 1993).

Theoretically, densitometry can be performed in any part of the skeleton, but conventional clinical practice established that bone mineral density assessment should be accomplished in the proximal femur or the lumbar column (the axial skeleton in the realm of densitometry), and for the diagnosis of OP should be considered the lowest *T-score* of the lumbar column, the neck of the femur or the total hip (Lewiecki *et al.*, 2004). Bone density in the forearm, calcaneus and total body can also be measured with DXA. Peripheral measurements can be good predictors of BMD but it seems prudent not to assume that they can diagnose osteoporosis as good as measurements in the axial skeleton (Bonnick, 2010).

Studies of BMD in the lumbar spine are probably the most common in clinical context but the proximal femur has received the preference in anthropological studies (e.g., Lees *et al.*, 1993; Curate *et al.*, 2013a; Mafart *et al.*, 2008; Mays *et al.*, 2006; Zaki *et al.*, 2009). Precision error is reduced, both in the lumbar column (~1%) and the proximal femur (1–3%). Nevertheless, the femur preserves generally better than the lumbar spine in archaeological contexts and its positioning in the densitometer is much simpler. The radius has also been used to assess bone loss in paleopathological studies (e.g., McEwan *et al.*, 2004; Zaki *et al.*, 2009) but BMD assessment at the forearm in archeological samples is shown to be highly problematic due to the frequent inability of the densitometer to detect bone mass at this location (Ferreira *et al.*, 2012). Although precise and reproducible, DXA measurements in archeological skeletal material can be distorted by taphonomic processes (Agarwal, 2008). Notwithstanding, there is a body of evidence (both direct and indirect) suggesting that diagenesis affects bone mineral content only marginally (Mays *et al.*, 1998; Mays *et al.*, 2006; Mays, 2008a; Turner-Walker & Syversen, 2002). The

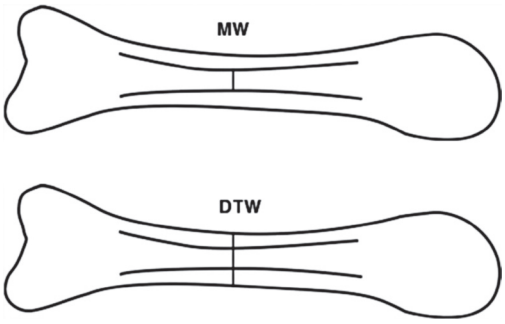

Fig. 7 - Cortical thicknesses taken at the middle of the diaphysis in tubular bones (DTW: diaphysis total width; MW: medullary width).

lack of soft tissues and bone marrow in historical skeletal remains also hinders DXA measurements (Brickley, 2000; Mays, 2008a) – a water bath or rice can be used as surrogates of soft tissue (Brickley & Agarwal, 2003; McEwan *et al.*, 2004) but comparisons with living individuals are thorny, and should be performed judiciously or even avoided

Radiogrammetry

Radiogrammetry quantifies the amplitude or geometry of cortical bone in tubular bones (usually computes the ratio between the medullary cavity thickness and the total width of diaphysis), through direct measurements in a plain radiograph (Ives & Brickley, 2004). Although ineffective to diagnose OP and assess fracture risk in individual patients, radiogrammetry is a valuable method to assess cortical bone loss in epidemiological settings (Boonen *et al.*, 2005; Yasaku *et al.*, 2009), and it is still widely used in studies directed to certain pathological conditions, like rheumatoid arthritis (Böttcher & Pfeil, 2008) or lupus erythematosus (Kalla *et al.*, 1992). This technique was introduced in the clinical literature in 1960, by different researchers (Barnett & Nordin,1960; Virtamä & Mahonen, 1960), also holding a long history in paleopathology (Ives & Brickley, 2004).

Conventional radiogrammetry only reveals modifications occurring in the cortical bone, i.e., periosteal apposition and, particularly, endosteal resorption (Adams *et al.*, 1969); being insensitive to early bone loss (Steiner *et al.*, 1996). The mineralized bone volume decay results in the reduction of calcium and radiographic absorption (Grampp *et al.*, 1997). The sites of resorption (endosteal, intracortical and periosteal surfaces) can react contradictorily to the different metabolical stimuli, and the subtle alterations in the endosteal envelope usually elicit challenging interpretations of cortical bone loss at this location. As such, while the measurement of total with is precise and reproducible, the direct measurement of the medullary width is less accurate (Bonnick, 2010). The precision of the method has been variously reported between 5 to 10%, depending on the measurement site, but in expert hands precision is greatly enhanced (Adams *et al.*, 1969; Ives & Brickley, 2004). The repeatability of radiogrammetric measurements in paleopathological studies is purportedly good (Mays, 2008a). Digital x-ray radiogrammetry (DXR) is more accurate and suitable for epidemiological studies than traditional radiogrammetry (Boonen *et al.*, 2005; Bötcher *et al.*, 2005), with results roughly comparable to DXA (Brown & Josse, 2002), but has not been used in paleopathological studies.

In the classical scheme, radiogrammetric measurements are taken from plain radiographs, with three basic steps to accomplish a radiogrammetric analysis: Acquire a long bone X-ray image, determine the cortical thicknesses in the (middle of the) diaphysis (Fig. 7), and compare the measurements with a reference scale. Detailed procedural guides for radiogrammetric analysis are given in Meema & Meema (1987) and Ives & Brickley (2004).

The second metacarpal has been used comprehensively in anthropological studies of cortical bone loss (e.g., Beauchesne & Agarwal, 2011; Ekenman *et al.*, 1995; Glencross & Agarwal, 2011; Ives, 2007; Lazenby, 1998; Mays, 1996, 2000, 2001, 2006a; Rewekant, 2001; Robb *et al.*, 2012). The circular morphology of the diaphysis (but see Lazenby, 1995 and Lazenby, 1998), the central positioning of the medullary canal and

the diminutive thickness of the surrounding soft tissues (Ives & Brickley, 2004; Mays, 2008a), combined with a good index of preservation in archeological samples (Lazenby, 1998), makes the second metacarpal an appropriate bone for radiogrammetric studies in paleopathology. Radiogrammetry of the femur and the tibia has also been utilized to assess age-related cortical bone loss in skeletal samples (e.g., Curate, 2009; Curate *et al.*, 2009; González-Reimers *et al.*, 1998; Mays *et al.*, 1998).

Other techniques

The first paleopathological studies focusing on bone loss employed direct measurements of cortical bone in the femur diaphysis (e.g., Armelagos *et al.*, 1972; Dewey *et al.*, 1969; van Gerven *et al.*, 1969). This method, albeit simple and inexpensive, is severely hampered by the requirement to destroy bone in order to measure cortical thickness.

Skeletal histomorphometry, the microscopic study of the properties, shapes, and measurements of bone tissue, is also a destructive technique (Stewart *et al.*, 2012). It allows a quantitative evaluation of morphological modifications at the tissue and cellular levels, identifying balance disruptions in bone remodeling (Brickley & Agarwal, 2003; Stewart *et al.*, 2012). The femur and the rib are the most common examined bones in paleopathological studies of bone loss and remodeling (e.g., Agnew & Stout, 2012; Cho & Stout, 2003; Cho & Stout, 2011; Ericksen, 1980; Martin & Armelagos, 1979; Stout & Lueck, 1995; Thompson & Guness-Hey, 1981) but the tibia has also been used (González-Reimers *et al.*, 2007). Adequate preservation of the bone microstructure is crucial in histomorphometric studies (Cho & Stout, 2003).

The macroscopical examination of radiographic images can provide helpful information regarding bone amount and structure (Brickley & Agarwal, 2003). With the Singh Index (Singh *et al.*, 1970) it is possible to give a score to the pattern of trabecular bone but the method's ability to evaluate bone loss is reduced and its repeatability is low.

Digital radiographic images, light microscopy or scanning electron microscopy capture the trabecular arrangement of bone, evaluating age-related changes in trabecular microstructure (Agarwal, 2001; Brickley & Agarwal, 2003; Roberts & Wakely, 1992). The assessment of trabecular connectivity refers to bone quality, a crucial aspect of bone health (Agarwal *et al.*, 2004; Agarwal, 2008).

Energy-dispersive low angle X-ray scattering (EDLAX) has some advantages over DXA: it generates an estimate of volumetric BMD, measures trabecular and compact bone, or just trabecular bone, and recognizes the different minerals in a bone sample (Brickley & Agarwal, 2003; Mays, 2008a). Unfortunately, the technique produces high radiation doses and cannot be used in clinical settings. As such, its availability is exceedingly reduced (Brickley & Agarwal, 2003).

Computed tomography is an imaging technique that involves a source of X-rays and quantitative computed tomography (qCT) also quantifies bone mineral content and assesses bone loss (Bruner & Manzi, 2006; Genant *et al.*, 2008; Guglielmi *et al.*, 2011) but, in contrast to DXA, qCT provides separate estimates of trabecular and cortical bone mineral densities and offers three-dimensional (volumetric) information about BMD (Genant *et al.*, 2008). CT scanners are large and expensive. As such, CT availability for the study of large skeletal series is somewhat limited. González-Reimers *et al.* (2007) examined bone density by qCT in Canarian pre-Hispanic samples (right tibia). qCT provided only a rough estimate of trabecular bone mass in the tibial samples, with the low accuracy attributed to the lack of soft tissues and the air bubbles confined within the trabecular bone.

Current problems and future directions

One of the greatest drawbacks in the study of OP in archeological samples pertains to the assessment of age at death in adult skeletal remains. Biological aging is extremely variable, and the appraisal of age at death usually renders

poor to mediocre estimates of biological and chronological age in adult individuals (Curate *et al.*, 2013a). Also, sex determination is not flawless, with error increasing in aged individuals (Walker, 2005). Of course, this produces challenging problems for paleopathological investigations of age- and sex-related diseases, like OP (Mays, 2006a).

The use of a wide array of methods for the assessment of bone loss in the past is baffling, wearying the power of anthropological comparative analyses (Agarwal, 2008; Brickley & Agarwal, 2003). However, different methods offer distinctive insights about bone remodeling and maintenance (Brickley & Agarwal, 2003), addressing central features of bone health other than bone mass, like bone quality, bone geometry or intraskeletal heterogeneity of bone mass. As the most common bone density measurement technology, and the gold-standard test to diagnose osteoporosis, DXA should be used routinely to assess bone mineral density in archeological samples. The effects of diagenesis and the difficulties in comparing results obtained in dry bone with those of living subjects do not transcend the advantages of the method, namely its precision and availability. Reference skeletal samples can be used for comparisons – for example, all adult individuas from the Coimbra Identified Skeletal Collection (mid 19th – early 20th centuries) and the Identified Skeletal Collection of the 21st Century – Santarém are currently being analysed with DXA. Hopefully, the densitometric data obtained in these collections will be available for comparison with archeological densitometric data.

The analysis of fractures in paleopathology requires the use of operational definitions of the so-called osteoporotic fractures, with special attention to the fractures of the vertebrae. Also, the descriptions must be comprehensive and systematic, following clinical and paleopathological protocols (e.g., Lovell, 1997; Müller, 1990; Redfern, 2010; Roberts, 2000). Historical studies of osteoporosis must address the association between bone mass and fractures. Likewise, additional bone features – such as bone quality or geometry – should be of consideration in the paleoepidemiology of fragility fractures (see e.g., Navega *et al.*, 2013; Sievänen *et al.*, 2007). For example, proximal femoral geometry is likely a risk factor for fractures of the hip (and also of the distal radius). Hence, the diachronic evaluation of bone geometry (with the support of traditional morphometrics or, rather, applying complex and powerfull shape analyses within the framework of geometric morphometrics) can contribute to the knowledge of the mechanisms that promote hip and distal radius fractures in contemporary populations.

The modern clinical understanding of osteoporosis has been strengthened by the insights produced by different scientific disciplines, such as paleopathology. In spite of enormous lifestyle dissimilarities, the epidemiological patterns of bone mass decrease in skeletal samples is, most of the times, similar to the ones observed in modern populations and, although the overall incidence of OP and related fractures is on the rise, it is now evident that OP is a malady with deep roots in the past. Osteoporosis also belongs to the «history of suffering» (in the faultless expression of Jacques Le Goff [1985]), a tragic narrative where individual horror merges with communal consciousness. Nevertheless, its immersion in history was, until recently, experienced only when associated with excruciating events such as fractures. The study of osteoporosis in past populations (with a *genus vitae* utterly different from the sociocultural conditions experienced by modern communities) supplements diachronic depth to the knowledge about bone modifications related to age, menopausal status or lifestyle. Notwithstanding, it is difficult to fill the gaps between the past and the present, and the knowledge about OP, contemporarily and in the past, must rely both on biomedical paradigms and on the holistic, comparative, analyses of biological anthropology.

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