Metabolic Disease

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Metabolic disease, or metabolic bone disease, represents a suite of conditions that cause an imbalance in normal bone remodeling processes. These conditions are of increasing interest to bioarchaeology (see BIOARCHAEOLOGY) as they lie at the intersection of human culture and health. By definition, metabolic diseases have nutritional, cultural, social, or genetic (see GENETICS: ANCIENT) causes rather than infectious ones. Yet some metabolic diseases can affect susceptibility to certain infectious diseases (see INFECTIOUS DISEASE), and others may arise as sequelae (i.e., consequential secondary conditions) spawned by a chronic infectious disease. Metabolic diseases can affect the whole body, as is the case with the general bone density reduction of osteoporosis, or may be limited to only a few focal areas, as with Paget's disease of bone. Bioarchaeologists use osteological (see OSTEOLOGY) evidence of metabolic disease found on human remains to infer genetic and cultural similarities, as well as social and sex-based differences, within past human populations.

Metabolic diseases are caused primarily by a deficiency or surplus of a particular mineral or hormone required in the formation or resorption of bone tissue. During bone modeling and remodeling, specialized osteoclast cells are signaled by cytokines, growth factors, and hormones to resorb bone. This is followed by the signaling of specialized osteoblast cells which deposit new bone matrix called osteoid. Osteoid is composed of the organic component of bone, including mostly collagen fibers, and the nonorganic hydroxyapatite, which subsequently mineralizes the matrix.

The main minerals implicated in bone homeostasis are calcium, phosphate, and magnesium, which all play a role in bone mineralization as the principal components of hydroxyapatite ($Ca_5(PO_4)_3(OH)$). Other necessary minerals less frequently implicated in problems of bone homeostasis include fluoride, sodium, potassium, strontium, and citrate. Often deficiencies in any of these minerals stem from dietary and environmental factors. The main hormones required for normal bone maintenance are vitamin D, estrogen, parathyroid hormone, and to a lesser extent calcitonin, thyroid hormone, and vitamin A. Deficiencies in many of these hormones result from normal age-related decreases in hormonal production, but can also result from environmental and dietary factors as well as certain congenital conditions (see CONGENITAL CONDITIONS) of metabolism. Many metabolic diseases cause similar patterns of nonspecific abnormal bone growth (i.e., periosteal reactions) or bone reduction (i.e., pitting), complicating the identification of the specific metabolic disorder in skeletal remains. The metabolic diseases described in detail in the paragraphs to follow include those identified in past populations through their unique skeletal manifestations.

Vitamin C is an important nutrient in immune response, absorption of iron, and the formation and maintenance of body tissues, especially collagen. It must be obtained from dietary sources, such as fresh fruits and uncooked vegetables. Vitamin C deficiency is known as scurvy, the consequences of which are dependent upon the age of the individual and the duration of the deficiency. Several symptoms arise as a result of the impaired collagen formation associated with scurvy. These include hemorrhaging, hemarthrosis (bleeding into the joints), hair loss, and depressed osteoblastic activity. The skeletal manifestations of scurvy that are visible in human remains from archaeological sites vary according to the age of the individual. In subadult individuals, chronic bleeding from scurvy can cause abnormal porosity of bone cortex (particularly affecting the sphenoid, mandible, maxilla, orbits, scapulae, and os coxae), new bone formation (affecting the orbits, cranial vault, long bone ends, and os coxae), dental enamel hypoplasias and antemortem tooth loss, and enlargement or fracture of ribs near the costochondral

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junction. In adults, scurvy can result in new bone formation in the orbits and the ends of long bones, antemortem tooth loss and alveolar bone inflammation, vertebral osteopenia and possible biconcave compression, and transverse fractures of ribs at the costochondral junction (Brickley and Ives 2008).

Due to the role of vitamin C in iron absorption and its association with internal bleeding, scurvy and anemia (see ANEMIA) often exist as co-morbidities, complicating attempts to separate symptoms and skeletal effects caused by each condition. Similarly, scurvy's influence on immune system fitness leads to co-morbidities with infectious diseases that cause nonspecific skeletal reactions such as periostitis and osteomyelitis. Thus, a cautious approach must be taken in the paleopathology (see PALEOPATHOLOGY) of scurvy, including the description of a combination of probable scorbutic lesions, the weighting of the more unique lesions such as sphenoidal porosity, and the use of a rigorous differential diagnosis (see DIFFERENTIAL DIAGNOSIS). The use of scanning electron microscopy, for example, has been shown to successfully distinguish between the expansive diplöe of anemic orbital porosity and the periosteal reaction characteristic of scorbutic orbital porosity (Brickley and Ives 2006).

Evidence of scurvy has been reported at archaeological sites globally, including in areas with surprisingly ample dietary sources of vitamin C in the natural environment. These discrepancies between expected and observed nutrition of ancient populations have been attributed to the role of social control and structural violence influencing nutritional variation within and between populations, as well as nondietary factors such as infectious disease and parasitism (see PARASITOLOGY) (Halcrow et al. 2014). In these cases, paleoethnobotany and stable isotope (see PALEOETHNOBOTANY AND STABLE ISOTOPES) evidence of diet may serve to narrow the etiology of scurvy. However, these cases of the appearance of scurvy in unlikely environments speaks volumes to the potential underreporting of scurvy cases in paleopathology where mild scorbutic lesions may be disregarded or misinterpreted, and scurvy not considered in differential diagnoses. Due to the challenges surrounding scurvy's co-morbidities, its often nonspecific skeletal manifestation, and potential for underreporting in the paleopathological literature, wider paleoepidemiological patterns of this metabolic disease in antiquity remain to be seen.

Vitamin D is necessary for immune reaction, mineral metabolism, cell growth, and cardiovascular health. It can be either produced by the body naturally through conversion of ultraviolet rays in the skin, or obtained through dietary sources such as dairy products. The deficiency of vitamin D, called either rickets or osteomalacia depending on the age of the individual, can cause hypocalcemia and poorly mineralized bone. As with scurvy, the skeletal manifestation of vitamin D deficiency varies according to the age of the person affected. In subadults, rickets causes delayed closure of fontanelles, thinned cranial bone, and frontal/parietal bossing, as well as layers of spiculated, irregular porous bone in the cranium. It also causes delayed dental eruption, hypoplastic defects, kyphosis or scoliosis of the vertebrae, enlargement of costochondral rib junctions and sternal protrusion, abnormal bending of the ribs, os coxae, sacrum, and long bones, and porosity, fraying, and enlargement of the metaphyses due to disorganized growth, which often leads to growth stunting. In adults, osteomalacia causes fine pitting of the cranium, antemortem tooth loss, kyphosis or scoliosis with biconcave compression of vertebral bodies, pseudofractures of the ribs and os coxae, long bones, scapulae, metacarpals, and metatarsals, and angulation or bending of the os coxae, long bones, scapulae, and ribs.

Evidence of rickets and osteomalacia has been reported at several archaeological sites, with most following the Industrial Revolution in the British Isles and northern Europe where manmade smog coupled with naturally limited sunlight during the winter months reduced the body's ability to manufacture vitamin D. As with scurvy, the effects of vitamin D deficiency on the skeleton are more severe in subadult individuals due to the mineral requirements of rapid bone turnover due to growth. The skeletal effects of rickets and osteomalacia may remain unnoticed in many cases, with very mild bending of the long bone shafts that only slightly enhances their normal bending morphologies. In environments allowing more ultraviolet ray exposure, these metabolic diseases of vitamin D deficiency may indicate cultural practices of prolonged breastfeeding (see

INFANT FEEDING) and inadequate exposure of high-social-class individuals to sunlight (Giuffra et al. 2015).

One of the most common metabolic diseases resulting from hormonal deficiency is osteoporosis. Osteoporosis describes a decrease in bone mass with subsequent increase in fracture risk associated with age-related decline in sex hormones of both men and women. Its skeletal manifestations include fine pitting, porosity, or thinning of the cranial vault, antemortem tooth loss or resorption of the alveolar margins, fractures of the vertebrae, ribs, pubic rami, distal radius, or femoral neck or trochanter, kyphosis, vertebral wedging, or biconcave deformities, and thinning of the ilia.

Osteoporosis can be difficult to identify with confidence in archaeological human remains. Several case studies have attributed skeletal changes to osteoporosis, but few studies have surveyed its presence at a populational level. Differential diagnosis of osteoporosis in paleopathology is complicated by its co-morbidity with scurvy and vitamin D deficiency, as well as its sometimes subtle skeletal manifestation (i.e., generally lightweight bones or noticeably dispersed trabeculae). Such a wider populational study could reveal influences of diet and activity level as evidenced by susceptibility to osteoporosis.

Paget's disease of bone refers to a chronic disease resulting in the disruption of bone remodeling in certain bones, characterized by skeletal enlargement. The cause of the disease is still uncertain, but it seems to have a genetic and perhaps infectious (viral) component. Its skeletal manifestations include enlargement or thickening of the cranial vault and vertebrae, hypercementosis or ankylosis of the teeth, fractures of vertebrae and long bones, deformities of the os coxae, bowing or widening of the long bones, and a bone surface texture similar to that of pumice stone.

Paget's disease of bone has rarely been identified in archaeological human remains, including at many sites in the British Isles, leading to the hypothesis that this disease originated in the region. Again, paleopathological reports of this metabolic disease have mainly consisted of case studies, with population-level prevalence unknown. Co-morbidities such as osteosarcoma co-occurrence with Paget's disease of bone are likewise unexplored in past populations. With more regional surveys and meta-analyses, bioarchaeologists are poised to offer key details of the potential environmental and genetic factors that play a role in the disease.

Fluorosis is a condition caused by the surplus of fluoride in the body due to the ingestion of toxic levels. Fluorine substitutes for the hydroxyl ion in the hydroxyapatite crystal of bone and teeth, forming fluoroapatite, a more brittle structure. Fluorine also stimulates osteoblastic activity. The skeletal manifestation of fluorosis includes thick, heavy, and irregularly shaped bones (particularly the cranium and long bones), ossification of soft tissue attachments, ankylosis of the vertebrae and ribs, and teeth with white patches and possible pitting.

Fluorosis has been reported from archaeological sites in North America and the Middle East. Again, careful differential diagnosis considering combinations of skeletal lesions and the inclusion of environmental and epidemiological evidence is necessary to pinpoint fluorosis in past populations. With advances in human skeletal geochemistry (see HUMAN SKELETAL GEOCHEMISTRY) and portable X-ray fluorescence spectrometry (pXRF) (see PORTABLE X-RAY FLUORESCENCE SPECTROMETRY (PXRF)), future analyses of fluorosis and other metabolic conditions may be bolstered by trace element analysis of bone, though caution must be taken to rule out confounding factors of postmortem mineral absorption from the soil.

Other, less common metabolic conditions include hyperparathyroidism, pellagra, starvation, hyperostosis, hypophosphatasia, osteogenesis imperfecta, and osteopetrosis. These conditions are not discussed here due to the rarity of their detection in human skeletal remains. Much is still unknown about the mechanisms and skeletal manifestations of metabolic disorders. With advances in clinical knowledge of the biological processes and effects of various chemicals on metabolism, bioarchaeologists will be able to identify more skeletal manifestations of metabolic disorders in osseous remains. Many metabolic bone diseases have overlapping skeletal manifestations, necessitating the use of multiple lines of evidence and differential diagnosis. With increased calls for increases in rigor in paleopathology, use of algorithmic methods

to account for lesion patterning in differential diagnosis, and incorporation of advanced imaging and mineral composition assays, metabolic bone disease is poised to feature more widely in future studies of skeletal pathologies and lifelong skeletal maintenance and well-being in past populations.

SEE ALSO: Malnutrition

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