

Skeletal and Metabolic Bone Disorders with special reference to African Americans

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Abstract

The human skeleton is living tissue that is either growing or being renewed. Our understanding of the pathogenesis of bone disorders has progressed considerably over the past 37 years. A large number of genetic and developmental disorders affect the skeleton. Rare bone diseases account for 5% of all birth defects. The skeletal dysplasias are inherited in an autosomal recessive, autosomal dominant, X-linked recessive, and X-linked dominant, and Y-linked manner.

Keywords: skeletal disorders; bone diseases; osteogenesis imperfecta; nosology; skeletal malformation syndrome

Introduction

The human body contains 206 bones and are living tissue. Older bone tissue is replaced with newly formed bone tissue in a process called remodeling. We commonly measure the condition of our bones by its density and our bone density peaks typically between the ages 25 and 30. Thereafter, as we continue to age, our bones gradually lose density. Genetic disorders of the bones are a large group of rare clinically distinct and genetically varied conditions that affect fetal bones as they develop in the uterus. The skeletal rare diseases such as Osteogenesis imperfecta (OI; also known as brittle bone disease), juvenile Paget's disease or osteopetrosis (marble bone or stone bone disease) are the three of the more than 400 developmental abnormalities of the skeletal system.

Metabolic bone diseases are caused by congenital defects of bone cells or by factors that alter bone cell function. Many of these rare diseases are hereditary caused by genetic mutations that can be passed on to children of affected patients. Fibrous dysplasia (FD) is a rare bone disease characterized by replacement of the medullary cavity with fibrous tissue. Gorham's-Stout disease (GD), also known as vanishing bone disease, is a rare genetic disorder characterized by bone resorption and localized lymphangiogenic proliferation (Radhakrishnan and Rockson, 2008). Fibrodysplasia Ossificans Progressiva (FOP) is a rare disabling autosomal dominant disease that is characterized by heterotrophic ossification in the soft tissues following a simple injury (Kaplan *et al.*, 2008). Melorheostosis is a rare genetic bone disease of unknown etiology in which patients exhibit bone dysplasia marked with benign sclerosis (Motimaya and Meyers, 2006). Multiple hereditary exostosis (MHE) is a genetic disorder marked by multiple cartilage-capped bony protuberances (osteochondromas) of the axial skeleton presenting usually before

twelve years of age (Kivioja *et al.*, 2000). Craniometaphyseal dysplasia (CMD) is an extremely rare genetic bone disorder characterized by overgrowth and progressive sclerosis of the craniofacial bones and flaring of the metaphyseal plates of femurs (Kirkpatrick, 1987; Cole and Cohen, 1988). Achondroplasia (chondrodysplasias) is a human bone genetic disorder of the growth plate and is the most common form of dwarfism (Horton *et al.*, 2007). Hypophosphatasia (HPP) is an inherited metabolic bone disorder caused by genetic loss of function mutations of tissue non-specific alkaline phosphatase (Ramadza *et al.*, 2009).

Diagnosis

The most common diseases or disorders that affect the bones are osteoporosis, Paget's disease, osteonecrosis, osteoarthritis, scoliosis and low bone density. Common symptoms include short bones of legs and/or arms, bowed or fractured bones, a small chest, abnormal ribs, duplication of fingers or toes etc. As the name implies, the disorders are due to genetic abnormalities. The cause may be linked to a dominant or recessive trait, or X-linked disorder, or a spontaneous gene mutation or fetal exposure to toxins or infections that interfere with normal skeletal development. Nosology Committee of the International Skeletal Dysplasia Society updated the tenth version of the Nosology which comprises 461 different diseases. Pathogenic variants affecting 437 different genes (92%) of genetic skeletal disorders.

Conditions in which skeletal development is compromised result in misshapen bones, called skeletal dysplasias. It is a complex group of bone and cartilage disorders with strong clinical and genetic heterogeneity. In other cases, the organic component of the bone tissue is affected, leading to decreased bone strength, as in the case of osteogenesis imperfecta. Genetic defects can cause the bones to become very thick but malformed

and brittle, as in the case of osteopetrosis. In some cases, the deposition of bone material is impaired, leading to bones that are too flexible and weak and are called rickets (which affects children) or osteomalacia (which affects adults). Patients with chronic renal disease are not only at risk of developing rickets and osteomalacia (Elder, 2002), but they are also at risk of a complex bone disease known as renal osteodystrophy (Cunningham *et al.*, 2004). Paget's disease of bone (Siris and Roodman, 2003) is a progressive, often crippling disorder of bone remodeling that commonly involves the spine, pelvis, legs, or skull. In the 2015 Nosology and Classification of Genetic Skeletal Disorders (GSDs) there were 436 GSDs with hundreds of causative genes (Bonafe *et al.*, 2015). Fetal skeletal dysplasia (FSD) comprises a complex group of systemic bone and cartilage disorders (Waratani *et al.*, 2020).

Osteoporosis are most commonly inherited in an autosomal dominant (AD) fashion but can be autosomal recessive (AR) or X-linked (XL) (Bollerslev *et al.*, 2013). The AD, AR and XL forms of osteoporosis are predominantly caused by mutations in the *CLCN7*, *TRIRG1* and *IKBKG* genes respectively. Between 85 and 90% cases are caused by mutations in *COL1A1* and *COL1A2* genes which code for type I collagen (Steiner *et al.*, 2014). Hypophosphatasia (HPP) is multi-systemic metabolic dysplasia inherited in autosomal dominant or recessive fashion, caused by loss of function mutations in the *ALPL* gene which encodes the tissue non-specific alkaline phosphatase enzyme leading to defective bone mineralization (Whyte, 2017). XLH, also known as vitamin D-resistant rickets is the commonest heritable and non-nutritional form of rickets. XLH is X-linked dominant bone dysplasia caused by *PHEX* gene mutations. Fibrodysplasia Ossificans Progressiva is an extremely rare and severely disabling autosomal dominant condition, in which damaged fibrous tissue turns into bone. It is caused by activating mutations in the *ACVR1* gene. The genetic basis of MHE has been identified due to mutations in the *exostosin-1*, *EXT1* and *EXT2* genes.

African Americans

The incidence of osteoporosis and related fractures in African American women is half that of Caucasian women. African American women who sustain osteoporosis-related fractures have increased disability and decreased survival. African American women begin menopause with higher bone mineral density (BMD) and have lower rates of women's bone loss after menopause, which account for their decreased incidence of osteoporosis and related fractures (Bohannon, 2009). Some studies in Caucasian and Asian women suggest that polymorphisms in the vitamin D receptor (VDR) gene are associated with BMD and the rate of postmenopausal bone loss. VDR gene polymorphisms are not associated with BMD or indices of bone turnover in the population of older African American women. DNA sequence variation in the VDR gene or a nearby locus may influence intestinal calcium transport and the rate of postmenopausal bone loss in African American women. African American children with Crohn's disease are more likely to have vitamin D deficiency compared to Caucasian with Crohn's disease, but have similar BMD. African Americans have a lower incidence of fractures than Caucasians, which has been attributed to a higher peak bone density in African Americans (Farmer *et al.*, 1984; Jacobsen *et al.*, 1990; Griffin *et al.*, 1992). BMD is inversely related to abdominal visceral and subcutaneous adipose tissue (Katzmarzyk *et al.*, 2012). It is becoming increasingly evident that suboptimal vitamin D (25OHD) serum levels are a common health problem. 25OHD insufficiency to be common in elderly African American women of low socioeconomic status.

Prevention & Treatment

BMD is under genetic control. The ways to combat this natural loss of bone mass are medications e.g., vitamins and minerals, estrogen replacement therapy, strength-training and weight-bearing exercises. If Paget's disease of bone is diagnosed early, impact can be minimized.

Silencing of the dominant allele in OI would result in a milder phenotype and attempts using siRNAs (small interfering RNAs), shRNA (short hairpin RNA) and antisense oligodeoxyribonucleotides (ODNs) have been promising.

Treatments and outcomes depend on the type and severity of the skeletal disorder. Rickets and osteomalacia are relatively uncommon diseases in the United States, since they can generally be prevented by ensuring adequate levels of vitamin D. Bone marrow transplant (BMT) is frequently an effective form of treatment for the recessive infantile form of osteoporosis. Fetal stem cell transplants are not new, with similar treatments attempted since the 1980's and for other conditions (thalassemia, sickle cell, severe immune deficiency).

Conclusion

Osteoporosis is a major public health problem with low bone mass affecting half the women aged 50 years or older. Evidence from various studies has shown that higher body mass index is a protective factor for BMD. Though African American women are less likely to have low BMD than White women, the increase in BMD with body mineral index seen in Caucasians is not seen in African Americans. Several studies have documented relationships between adipose tissue and BMD. The explosion in molecular genetics has allowed for gene identification in more than two thirds of the skeletal dysplasias. Genetic counseling is recommended for affected individuals and their families. Should the trial of fetal stem cell transplants be successful it opens a whole new world for treatment of many different disorders. Thus the door is open for further technologies dealing with the root genetic change.

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