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Original Article

Osteoporotic Vertebral Fractures as Part of Systemic Disease

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Abstract

Our understanding of the genetic control of skeletogenesis and bone remodeling is expanding, and normally, bone resorption and bone formation are well balanced through regulation by hormones, growth factors, and cytokines. Osteoporosis is considered a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue. Consequent increased bone fragility results in higher fracture risk. The most common osteoporotic fractures are located in the spine, and they form a significant health issue. A large variety of systemic diseases are associated with risk of osteoporotic vertebral fractures, illustrating its multifactorial etiology. Prevalences of these conditions vary from common to extremely rare, and incidence peaks differ according to etiology. This review appreciates different aspects of osteoporotic vertebral fractures as part of systemic disease, including genetic, immunologic, inflammatory, metabolic, and endocrine pathways. It seems impossible to be all-comprehensive on this topic; nevertheless, we hope to provide a reasonably thorough overview. Plenty remains to be elucidated in this field, identifying even more associated diseases and further exposing pathophysiological mechanisms underlying osteoporotic vertebral fractures.

Key Words: Genetics; osteoporosis; spine; systemic disease; vertebral fracture risk.

Introduction

Osteoporosis is considered a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Our understanding of the genetic control of skeletogenesis and bone remodeling is expanding. Normally, bone resorption and bone formation are well balanced and regulated by hormones, growth factors, and cytokines. Various internal and external factors are known to contribute to the risk of osteoporosis, illustrating the multifactorial etiology of the condition. The most well-known clinical risk factors for osteoporosis and fractures include age, lower body mass index *(1)*, immobility *(2−4)*, smoking *(5)*, alcohol consumption *(6)*, and glucocorticoid use *(7)*. In addition, a positive family history confers an increased risk of fracture *(8)*. The term secondary osteoporosis refers to disorders that are strongly associated with osteoporosis *(9)*; these include diseases with systemic inflammation such as rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), but also diabetes, hypogonadism (including premature menopause), malnutrition, and malabsorption. Medication use may also predispose to elevated fracture risk, but, this is beyond the scope of this review. This list is all-but comprehensive and, undoubtedly, many more risk factors and associated diseases are to be discovered.

Vertebral fractures are the most common osteoporotic fractures, and they are often a first manifestation of osteoporosis. These fractures represent a significant health issue *(10,11)* as they are associated with a high morbidity, including but not limited to acute and chronic pain, loss of independence, height

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loss, kyphosis, depression, higher risk of additional future vertebral and nonvertebral fractures (12−17), and increased mortality (18,19). There may be skeletal site−specific effects of fracture determinants, meriting the study of vertebral fractures apart from nonvertebral fractures, as we will discuss later in this review. Risk factors that have been specifically validated for incident vertebral fractures include prevalent vertebral fractures, older age, female gender, lower body height and weight, smoking history, and use of a walking aid (20,21). Very recently, Schousboe et al pioneered in prediction models for osteoporotic vertebral fractures in older men (22) and women (23), and although promising yielding area under the receiver operating curves of up to 0.69, validation in independent studies is needed, and future research may identify additional risk factors that enhance prediction of incident osteoporotic vertebral fractures.

This review appreciates different aspects of osteoporotic vertebral fractures as part of systemic disease, touching on genetic, metabolic and inflammatory pathways, and organ system dysfunction.

Structural Vertebral Deformities and Fractures

Several methods for radiological assessment of vertebral fractures exist, but a gold standard is lacking (24). Traditionally, conventional radiography has been the imaging modality of choice. Yet, 2 advantages of dual-energy X-ray absorptiometry (DXA) over conventional radiography for vertebral fracture assessment are the lower radiation dose and capture of the whole spine in 1 image with virtually no divergent radiation beam issues, particularly because DXA imaging resolution has improved drastically with the introduction of state-of-the-art machinery. Another novel add-on to DXA is the trabecular bone score (TBS), a measure of bone texture, which correlates with 3D parameters of bone microarchitecture reflecting bone quality and which is partly independent from DXA-measured lumbar spine bone mineral density (LS-BMD; 25). In any case, a number of differential diagnoses remain that complicate the diagnosis of vertebral fractures, including degenerative diseases, anatomical variation, and anomalies (26). More is becoming clear about these conditions and the possible presence or absence of an interrelationship with osteoporosis and associated fractures, as discussed in the following section. Therefore, we start the review by discussing the definition of osteoporotic vertebral fractures and mimickers of that should not be confused with vertebral fractures.

Nonfracture deformities represented by anatomical variation and developmental abnormalities have been reviewed extensively by Ferrar et al (27). From a lateral view, the spine has a natural curvature. Vertebrae in the mid-thoracic region are more wedge shaped, causing a mild kyphosis. Lumbar vertebrae have a relatively shorter posterior height and tend to be biconcave resulting in a normal lordotic curve. Some individuals have developmentally smaller or shorter vertebrae, particularly in anterior height found most commonly in the mid-thoracic region. This is thought to be due to congenital variation or as the result of inhibited growth of the vertebral body during childhood or adolescence, and it is also thought that these variants should not be regarded as fractures (28). In so-called ''step-like'' or ''step-off'' end plates, the central end plate is deeper with an abrupt transition to the more normal periphery. This is in contrast to the appearance of the fractured end plate in osteoporosis, in which, a smooth, concave depression extends from corner to corner of the vertebral body (27). These ''step-off'' end plates seem to be the consequence of a growth retardation in the central portion of the end plate due to central circulatory stasis. In contrast, the periphery of the growth plate has a different blood supply through short arteries, in which vaso-occlusion and microinfarction may lead to avascular necrosis and further developmental disruption of the vertebral body (29). Diseases that have been listed as associated with these observations are Gaucher's disease, hemolytic anemias including hereditary spherocytosis, sickle cell, and thalassemia hemoglobinopathies (30). The cortical margins of the inferior end plates of predominantly lumbar vertebral bodies L3 to L5 frequently have paired parasagittal concavities when viewed in the frontal projection, resembling the curvature of an aimed bow (31). When viewed in the lateral projection, the concavities are superimposed and lie in the posterior portion of the vertebral body and could then be confused with fractures (27). This aspect, called ''Cupid's bow'' is considered a normal anatomic variant. Histologic examination in cadavers showed thickened bone in the Cupid's bow end plate with annular fibers inserting into this region, which was detected at multiple lumbar and thoracic levels, with the highest frequency in the lower lumbar spine (32). Furthermore, the end plates tend to become progressively deeper with lower vertebral level, and another commonly seen normal variant is a deep inferior end plate. Another developmental variation is represented by balloon discs, where there is an occurrence of an unusually concave disc-vertebral border at multiple levels. A Japanese study has reported a prevalence of up to 14% in the healthy population, with an association with male gender and height, but a lack of a relation with back pain or age (33); yet, to our knowledge, no replication and validation studies have been published.

A specific example of an anatomical anomaly of the vertebrae that could be confused with vertebral fractures is Scheuermann's disease. With reported prevalence rates of up to 10%, the disease is frequently mentioned in the differential diagnosis of osteoporotic vertebral fractures (27). It is a form of osteochondrosis of the spine characterized by increased posterior rounding of the thoracic spine in association with structural deformity of the vertebral elements (34,35). Scheuermann's disease often first appears during adolescence at the time of puberty, resulting in permanent vertebral distortion and back pain in many cases. The etiology is unknown, but, genetics most likely plays a significant role (36); genetic surveys are underway. Scheuermann's disease is diagnosed on the basis of radiographic criteria of which those defined by Sørensen and Sachs are the most commonly applied: a thoracic kyphosis greater than 45°; at least 3