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Osteoporosis: From osteoscience to neuroscience and beyond

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ABSTRACT

Osteoporosis is well known to be a poly-factorial skeletal disorder characterized by a low bone mineral density (BMD) at which the risk of developing fracture is remarkably increased and affecting both the quality and quantity of life. Although it is nearly 180 years, since its first pathological identification, there is no effective cure against such aging-associated health concern. Traditional research direction on osteoporosis was mainly focused on the balance between bone formation and resorption, in which osteoblast and osteoclast physiology as well as a variety of relevant molecular factors underlying bone homeostasis have been intensively studied. Due to the knowledge advances in the field, more potential candidate factors/target genes involved in the regulation of bone homeostasis have been identified. Representative examples included the new roles of osteocytes in bone homeostasis and endocrine functions. Additionally, the muscular and nervous system also seem to play a regulatory role in bone homeostasis. After all, these new findings have paved novel directions in osteoporosis research. This review is aimed to provide an overview on the current accepted concepts of osteoporosis-associated bone physiology and its potential research directions in the near future.

Contents

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1. Introduction

Since the first recognition of its pathological appearance in 1835 by Lobstein (Lobstein, 1835), osteoporosis or its milder form osteopenia (Greek: *osteo* means "bone", *poros* means "passage, pore", *penia* means "loss") is now recognized as a low-BMD-associated bone disease with a poly-factorial etiology and is usually linked to the aged individuals (particularly female) (Mattingly and Pillare, 2009; Lau and Guo, 2011; Clarke and Khosla, 2010). This disease is commonly believed to be asymptomatic in nature prior to bone fracture and affects approximately 30% of women and 8% of men who aged over 50 years in the Western societies (Mattingly and Pillare, 2009). To this day, osteoporosis will be diagnosed as positive if BMD $\geq$ 2.5 standard deviations (for both male and female) below peak bone mass of 20-year-old healthy female average measured by dual energy X-ray absorptiometry (DXA) (Mattingly and Pillare, 2009; Kanis, 2002; Kanis et al., 2008), i.e., *T* score < −2.5 SD (Table 1). It is important to note that if a male reference range was used to derive the diagnostic threshold, the apparent prevalence of osteoporosis in that corresponding group would rise (Kanis et al., 2008). In addition to DXA, other diagnostic instruments may be used to provide further clinical details of bone structure. For example, quantitative computed tomography (QCT) scanning is used to assess information that is not available with DXA, e.g., bone volumetric density, geometry, size, and structure at multiple skeletal sites (Clarke and Khosla, 2010). Additionally, conventional magnetic resonance imaging (MRI) can be used to overcome projection errors as in the case of scoliosis and sagittal obliquity (Mattingly and Pillare, 2009).

As the poly-factorial bone disorder, osteoporosis is affected by but not limited to hormones (including steroids), growth factors, immunological status, sex, race, nutrition, physical activity, morbidity, treatment received (including smoking and alcohol intake), and especially aging (Lau and Guo, 2011; Clarke and Khosla, 2010; Osteoporosis in Men, 2012). Under normal aging, both sexes start losing areal bone mineral density (aBMD) at relatively slow rates at around the age of 40. Interestingly, women start losing aBMD and trabecular BMD (vertebrae, pelvis, and ultradistal wrist) more rapidly than men at around the age of 50 (onset of menopause) at which women experience a dramatic loss of gonadal sex steroid secretion (Clarke and Khosla, 2010). However, the loss of cortical bone in the long bones and vertebrae is less rapid than the loss of trabecular BMD at the same time point until around the age of 60 (8–10 years after menopause) at which this slower age-associated bone loss becomes prominent and continues for the rest of life (Clarke and Khosla, 2010). As a result, osteoporosis is commonly regarded as an age-associated osteopathic disorder, especially in postmenopausal women.

In the pathological perspective, osteoporosis can be classified into two main types: primary (usually linked to gender and age) and secondary (usually not linked to gender nor age but medical disorders) while primary osteoporosis can be further classified into two subtypes: senile (caused by age-associated bone loss) and idiopathic (caused by unknown reasons) (Mattingly and Pillare, 2009; Lau and Guo, 2011; Osteoporosis in Men, 2012). As osteoporosis significantly increased the risk of mortality (Johnell et al., 2004) and placed an enormous financial burden on different countries, e.g., the estimated annual direct health care expenditure for osteoporosis in US was 14 billion, in UK was 1 billion and in Australia was 7.4 billion in local currencies (Mattingly and Pillare, 2009), this public health concern shall not be overlooked. As a result, it is imperative to investigate into its pathological and pathogenic mechanism in order to acquire more insights for the development of better diagnostic and therapeutic interventions.

This review is aimed to provide an overview on the current accepted concepts on osteoporosis-associated bone physiology focused mainly at the cellular and molecular level. In the following sections, we will start first with the traditional view on osteoporosis and the commonly accepted pathogenic/physiological factors on bone homeostasis. Then, follow by the relationships between the skeletal system and other non-osseous tissues. Finally, impacts of these non-osseous systems on bone physiology will be discussed.

Table 1
Diagnostic criteria for osteoporosis by World Health Organization (WHO). BMD: bone mineral density; and SD: standard deviation (Mattingly and Pillare, 2009; Kanis et al., 2008).

Condition	Diagnostic criteria
Normal	BMD < 1 SD of a young normal adult reference value
Osteopenia	1 < BMD < 2.5 SD below that of a young normal adult reference value
Osteoporosis	BMD $\geq$ 2.5 SD below that of a young normal adult reference value
Severe osteoporosis	• BMD $\geq$ 2.5 SD below that of a young normal adult reference value • With 1 or more fractures

2. The commonly accepted concept on bone homeostasis

Adult human bone is consisted of various tissues including the osseous tissue (also known as the bone tissue), cartilage, dense connective tissues, epithelium, adipose tissue, and the nervous tissue (Tortora and Derrickson, 2012a). Osseous tissue alone occupies approximately 18% of the weight of the human body, and the skeletal system is consisted of the cartilages, ligaments, and tendons in addition to the entire framework of bones (Tortora and Derrickson, 2012a). Anatomically, human bones can be classified into: (Tortora and Derrickson, 2012b; Marieb et al., 2014) (1) long bone; (2) short bone; (3) flat bone; (4) irregular bone; and (5) sesamoid bone. Although the functions of bone are largely determined by their shapes, it is commonly believed that bones serve mainly but not limited to the following functions: (Rodan, 1998,b; Tortora and Derrickson, 2012a,b; Marieb et al., 2014) (1) mechanical support of soft tissues; (2) protection of the most important internal organs from mechanical injury; (3) assistance in muscle actions; (4) mineral homeostasis by storage and release of several mineral ions (especially calcium and phosphorus); (5) housing and support of hemopoiesis; and (6) energy storage and metabolism.

2.1. Osseous tissue, the complex matters

Osseous tissue consists of an abundant extracellular matrix surrounding the bone-dwelling cells (Tortora and Derrickson, 2012a). Such matrix is composed of approximately 15% water, 30% collagen fibers, and 55% crystallized mineral salts (predominately calcium phosphate; Tortora and Derrickson, 2012a). While the bone's rigidity is determined by the crystallized inorganic mineral salt components (predominately hydroxyapatite), the bone's flexibility is determined by the flexible components (comprising of type I collagen, proteoglycans, and a number of non-collagenous proteins; Tortora and Derrickson, 2012a; Brandi, 2009). It is important to note that osseous tissue is normally porous and the spaces within the bone are commonly serve as: (Dallas et al., 2013; Tortora and Derrickson, 2012a; Marieb et al., 2014) (1) channels for bone cell networks; (2) channels for blood vessels and nerves; and (3) storage sites for bone marrows.

For most of the osseous tissues, bone regions may either classify as cortical or trabecular type (also known as the compact type and spongy/cancellous type, respectively) depending on the size and distribution of the spaces (Tortora and Derrickson, 2012a; Marieb