Clinical Biochemistry 47 (2014) 950–959

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Osteoporosis in men

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ARTICLE INFO

Article history:
Received 8 December 2013
Received in revised form 24 March 2014
Accepted 29 March 2014
Available online 12 April 2014

Keywords:
Osteoporosis
Osteopenia
Men
Fracture-risk
Bone markers
Bone remodeling
Bone turnover
Bone resorption
Bone mineral density
Gonadal steroid hormones

ABSTRACT

Osteoporosis in men causes significant morbidity and mortality. Bone health declines gradually, often insidiously; and in light of the advancing aging population poses a serious public health issue that is not well recognized. Studies of the past decade have expanded our understanding of the events within, as well as the regulation of, bone remodeling and provided better insight into the physiology and pathophysiology specific to the adult male skeleton. The clinical measurement of bone mineral density using dual-energy X-ray absorptiometry remains the gold standard for diagnosis of osteoporosis in males; and fracture risk assessment is now recognized as a preferred approach to guide treatment decisions. Utilizing surrogate end-points such as increasing bone mineral density and decreasing concentrations of bone resorption markers, clinical trials have demonstrated efficacy in pharmacological treatment of osteoporosis in the adult male. Unfortunately, few studies have evaluated the anti-fracture benefits in this population. Measurement of bone turnover markers may be an additional tool to monitor therapeutic responsiveness in addition to the measurement of bone mineral density.

Introduction and epidemiology

Is osteoporosis in the adult males an insidious disease, or has insidious attention been given to this serious public health issue? These questions are quite reasonable given the prevalence of osteoporosis in men worldwide and the impact of the disease on this population. Consider, for example, that data acquired from various surveys suggest that the disease is estimated to affect more than 2 million men in the United States (US) [1], 5.5 million adult males across the 27 countries of the European Union [2], and 8.5% of otherwise healthy males over age 50 years in India [3]. Unfortunately, the full impact of the disease on this population is somewhat elusive due to, in part, the continued lack of its recognition by health care providers and its somewhat unclear diagnostic criteria [4].

Osteoporosis is characterized by a decline in bone mass and strength resulting from derangements in bone remodeling. The disease and a related condition, osteopenia, are defined by measures reflecting these changes, or the occurrence of a fragility fracture. Specifically, the diagnosis is made using measures of bone mineral density (BMD) with the comparison of the patient to a reference population (Table 1). This becomes important with the recognition that aging men, i.e., those <80 years, tend to lose BMD gradually, often silently, at a rate of approximately 0.5–1% per year [5,6]. When this loss begins it is quite variable and depends upon many factors such as ethnicity, geography, and overall health [7]. Data from the National Health and Nutrition Examination Surveys of 1988–1994 and 2005–2006 suggest that the prevalence of low BMD within the population has remained relatively constant since the late 1980s and that the prevalence of osteopenia may exceed that of osteoporosis ten-fold [8,9].

A consequence of both osteopenia and osteoporosis is an increased risk of fracture, particularly fragility fractures which occur with little or no apparent trauma and are often difficult to assess. Fragility fractures are by definition "caused by injury that would be insufficient to fracture a normal bone … the result of reduced compressive and/or torsional strength of bone" [10]. Estimates suggest that fractures stemming from the development of the disorder in adult males account for nearly 30% of fractures in both the USA and Canada and 39% globally [11,12]. Although adult males have an advantage of achieving higher baselines of bone density, they are also associated with a greater likelihood of fracture from their activities. Thus, a fracture that occurs because of osteoporosis may not be recognized as such which means osteopenia and osteoporosis are all too often "silent" [13]. This, unfortunately, adds additional layers of complexity and costs.

For men, osteoporosis is associated with increased morbidity and mortality, specifically following a fracture. This relationship is complex depending on multiple factors including comorbidities, the fragility of the individual, and even the implementation of measures to prevent fractures, i.e., fall prevention. Nevertheless, the impact of osteoporosis to the individual, their family, and society is significant. The Canadian

Abbreviations: BMD, bone mineral density; BMC, bone remodeling compartment; RANKL, receptor activator NFκB ligand; M-CSF, macrophage-colony-stimulating factor; TGFβ, tumor growth factor-beta; IGF-1 and -II, insulin-like growth factors I and II; BMPs, bone morphogenetic proteins; OPG, osteoprotegerin.

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http://dx.doi.org/10.1016/j.clinbiochem.2014.03.026
0009-9120/

Table 1
Definitions of osteoporosis and osteopenia based upon bone mineral density.

Normal: T-score not less than 1 standard deviation below the young adult mean value
Osteopenia: a T-score between 1 and 2.5 standard deviations below the young adult mean value
Osteoporosis: a T-score exceeding 2.5 standard deviations below the young adult mean value

Multicenter Osteoporosis Study showed that the occurrence of incident fractures in this population brought adverse changes in quality of life, including deficits in self-care, mobility, and ambulation [14]. The Rotterdam study raised awareness of the impact of osteopenia when their data showed that after age 55 years, osteopenic men were more likely to sustain a vertebral fracture compared with men with osteoporosis (61% and 21%, respectively) [15]. It should be noted that this increased rate is not due to increased risk but rather because of the number of men who have osteopenia. As implied earlier, younger, osteopenic men may not be diagnosed and those who know they have osteoporosis may take precautions to prevent trauma. One frequently assessed parameter is that of the relative risk of a second fracture. Whether this population is more likely to sustain a second fracture is unclear as some studies find adult osteoporotic males at greater risk compared to comparable females, while others do not [16–18].

These outcomes have significant economic impact when one considers the current rise in the aging population and gains in lifespan: The economic burden of osteoporosis is only expected to increase [12,19]. Based on estimations in 2005 by Burge et al., men account for 29% fractures and 24% of the total costs (~$4.1 billion USA) per year. Some estimates project these costs to rise by ~30% in this population over the next ten years [12]. Given these findings, efforts in elucidating the underlying mechanisms, identification and clinical management of men at increased risk of osteopenic- and osteoporotic-related fractures are increasingly important.

Although osteoporosis is well-recognized as a complex disorder of bone remodeling with considerable advances in the diagnosis and treatment of osteoporosis in women, the underlying mechanisms and clinical management of osteoporosis in men remain elusive. The aim of this review is to describe the recent advances in the understanding of the coordinated action between cells within the bone tissue and hormonal regulation of bone remodeling, describe recent insights into the physiology and pathophysiology of the male skeleton, as well as to describe recent progress in methods used for the diagnosis of the disorder in men, and the monitoring of therapeutic responsiveness.

Recent developments in bone metabolism

To understand osteoporosis, one must have a foundation in basic bone metabolism. This dynamic tissue is comprised of matrix and three cell types: osteocytes, osteoblasts, and osteoclasts. These cells respond to numerous hormones and biochemical events to coordinate bone resorption and formation for continual self-regeneration of bone tissue, a process collectively referred to as bone remodeling. This process is essential to ensure correct mineral homeostasis and maintenance of bone structural integrity.

Bone remodeling takes place in localized sites referred to as the bone remodeling compartment (BMC) [20,21]. One of the first events to occur involves the release of collagenase by osteoblastic-lineage lining cells to digest the thin-layer of non-mineralized matrix at the endosteal surface lining the bone marrow cavity [20]. The lining cells subsequently separate from the underlying osteocytes creating a resorption bed for osteoclastic resorption of the exposed mineralized matrix with a canopy layer of lining cells. The mechanisms regulating lining cell preparation of the BMC remain unclear; however, an intact canopy of lining cells appears to be important in the modulation of osteoclast and osteoblast functions [21]. As will be discussed shortly, it should be noted that the canopy lining cells border the bone marrow cavity and nearby capillaries.

Osteocytes are terminally-differentiated osteoblasts that comprise more than 90% of all bone cells [22]. These cells are embedded throughout mineralized bone matrix and play a key role in mineral exchange and matrix synthesis [23]. Growing evidence supports an important role of osteocytes in controlling bone remodeling [23–25]. Morphologically, these cells display unique, long dendritic-like projections that are thought to be mechanosensors used to detect mechanical stress, as well as "microcracks" in high bone turnover pathologies [23,24]. Active osteocytes secrete transforming growth factor-β (TGF-β) and osteoprotegerin (OPG), each being an inhibitor of osteoclastogenesis and/or osteoclastic resorption. On the other hand, under conditions of mechanical stress and microdamage, osteocytes undergo apoptosis with the release of receptor activator NFκB ligand (RANKL), a stimulator of osteoclastogenesis [23]. Thus, osteocytes appear to promote osteoclast resorption of deteriorated bone matrix in microdamaged areas through a RANKL-mediated mechanism [23–25]. Additionally, osteocytes highly express sclerostin which is a negative regulator of the Wnt/βcatenin pathway, a signaling cascade that is essential for osteoblast activity and bone formation. Sclerostin expression has been reported to be reduced in osteocytes upon mechanical loading, suggesting that osteocytes also play an important role in modulating osteoblast-mediated bone formation [23,26].

The second type of bone cell, osteoclasts originate from precursor cells of hematopoietic origin. Upon stimulation by RANKL and macrophage-colony-stimulating factor (M-CSF), the osteoclast precursor cells undergo osteoclastogenesis as they migrate into the area primed for resorption where they differentiate into bone-resorbing osteoclasts. Osteocytes are an important source of RANKL, though other cells in the microenvironment likely contribute to the available pool of the ligand [25]. It is unclear how osteoclast progenitors gain access to the resorption bed but it is likely through the migration of the progenitors from the nearby capillary bed via the canopy lining cells in a process similar to cell extravasation through an endothelial cell layer into tissue [20,21]. Mature osteoclasts are large multi-nucleated cells which attach to the resorption bed surface via podosomes to form a sealing zone. The sealing zone localizes and restricts the osteoclast resorption activity to the exposed mineralized matrix area immediately below the cell preventing damage to neighboring bone tissue [20]. Attached osteoclasts synthesize, and secrete a mixture of hydrogen and chloride ions forming an acidic microenvironment which is important for activation of proteolytic enzymes released by osteoclasts. One such enzyme is cathepsin K, a lysosomal cysteine proteinase that degrades type I collagen matrix [27]. The resulting clearance of microdamaged bone tissue and development of the resorption pit sets the stage for restoration of the lost bone via osteoblast-mediated bone formation.

Lastly, osteoblasts develop from mesenchymal stem cells to mediate bone formation via the synthesis and deposition of extracellular matrix at the resorbed cavity [20]. Osteoclasts appear to play an important role in the localization and activation of osteoblasts through both indirect and direct mechanisms. Various factors, such as TGFβ, insulin-like growth factors I and II (IGF-1 and -II), as well as bone morphogenetic proteins (BMPs), released from the bone matrix during resorption promote osteoblastogenesis and/or activity [20,25]. Direct modulation of osteoblast differentiation also occurs in response to direct cell–cell contact between osteoclasts and osteoblasts: Osteoclast expressed ephrinB2 binds to EphB4 receptors on the osteoblast cell surface, leading to bi-directional crosstalk with attenuation of osteoclastogenesis and enhancement of osteoblast differentiation [25,28]. Upon osteoblast differentiation and activation, osteoblasts produce extracellular matrix containing collagen type I and various non-collagenous proteins including osteocalcin, osteonectin, osteopontin and others, which form an osteoid layer filling the resorption pit [27]. As mentioned previously, osteocytes may play an important role in terminating osteoblast-mediated osteoid formation through production of sclerostin which antagonizes the Wnt/βcatenin pathway in osteoblasts [23,26]. The