Osteoporotic Fracture and Systemic Skeletal Disorders

Mechanism, Assessment, and Treatment

Hideaki E. Takahashi
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This book is dedicated to
Harold M. Frost, M.D.
A superb clinician, an enthusiastic teacher in orthopedic surgery, and an inspirational theoretician and mentor in bone biology.

and

Webster S. S. Jee, Ph.D.
A most zealous researcher, a keen teacher in anatomy and radiology, and a generous educator in musculoskeletal research.
This book would not have been published without their patient mentorship of the authors in areas related to bone physiology, histodynamics, and biomechanics, and their enthusiasm for understanding how the details of bone adaptation could be translated to improvements in human health.

Foreword

In the past, even very recently, osteoporosis and fragility fractures have been something of a Cinderella among medical subspecialties. Cardiovascular disease, cancer, neurological and endocrine disorders have commanded much more attention and priority, although their prevalence and the costs of their management are no greater. Perhaps it is because the incidence of fragility fractures is so tightly related to age that it was easy to see osteoporosis as a "natural" consequence of aging—not a disease at all—and thus not deserving of serious medical attention.

Well, that mindset is changing—of necessity. The world population is growing fast, despite the birth rate being at an all-time low. The aging population has two consequences of relevance here: one, that the incidence of fragility fractures, particularly hip fractures, is rising at an alarming rate—in all countries, but especially in the emerging economies—and that current trauma systems simply will not be able to cope. And two, that the ratio of older people to younger, working people, who support them, is changing dramatically—from around 5% in previous centuries to 50% or more in the twenty-first century, putting serious strain on the very fabric of society. There is nothing we can do about the age structure of the population, so the only solution is to maintain mobility, functional capacity, and independence to a greater age; thus alleviating this Dependency Ratio. A decent level of musculoskeletal function is essential for maintenance of independence; preventing as many fragility fractures as possible and treating those that do occur with high quality acute care and rehabilitation makes a big contribution.

So one of the many things the world needs right now is a good scientific and clinical evidence base on which to realize the potential benefits to patients and the whole of society of better prevention and treatment of fragility fractures. This book addresses that need.

A key aspect of the book's approach is to emphasize basic mechanisms—of maintenance of bone architecture and its malfunction in osteoporosis and other metabolic bone disorders; of the propensity to fracture that these generate; of how such fractures can heal and why they sometimes don't. When it comes to our ability to intervene usefully, again, it is the principles that dominate: of how bone health and structure can be measured, of the various pharmacological strategies for addressing osteoporosis, of how sarcopenia may be addressed to mitigate the risk of injurious falls—all things that allow the reduction of future fracture risk.

The final part demonstrates the strong orthopedic origins of the book, covering in practical terms the management of incident fragility fractures, particularly the main sources of disease burden: hip and spine fractures. But the approach is not that of a purely surgical manual; the importance of a team approach that covers the *frailty* of older fracture patients as well as the *fragility* of their bones is given full expression. Taken together with the earlier chapters on osteoporosis treatment and falls prevention, this means that the book covers all aspects of post-fracture care.

It is to be hoped that the promotion of a science-based approach to the global challenge of fragility fractures that this book embodies will be effective in preparing us to meet that challenge convincingly.

Fragility Fracture Network
Zurich, Switzerland

David Marsh

University College London
London, UK

Profiles

Harold M. Frost, M.D. (1921–2004)

An orthopedic surgeon who did his early work at the Henry Ford Hospital in Detroit, and subsequently at the Southern Colorado Clinic in Pueblo, Colorado. He was an active adjunct professor of Anatomy at Purdue University and Radiobiology at the University of Utah School of Medicine. He was the most influential theoretician in skeletal biology, laying the groundwork for much of what we now know about bone modeling and remodeling. His main contributions were the development of techniques to make quantitative measurements on non-decalcified bone sections and the invention of bone histomorphometry; discovery of the basic multicellular unit; the experimental demonstration that estrogens reduce bone turnover; the demonstration of microcracks in bone; a concept of Activate-Depress-Free-Repeat treatment; basic theories surrounding bone growth plate adaptation to mechanical loading; and the "mechanostat theory" of bone adaptation to mechanical stimuli. He developed the Utah Paradigm of skeletal physiology with W.S.S. Jee, and was a recipient of the ASBMR's highest research award, the Neuman Award (2001).

Webster S. S. Jee, Ph.D.(1925-2018)

He was the Director of the Radiobiology Bone Group/Laboratory and a Professor of Anatomy at the University of Utah for over forty years. He was a pioneer in the field of pre-clinical bone biology and pharmacology. His research topics included the early investigation of the hematogenous origin of osteoclasts; development/preclinical testing of the concept of reversing low bone mass with an anabolic agent and then preserving the new bone with an anti-resorptive agent, which is now used clinically; and the biokinetics and pathology of alpha-particle emitting radionuclides. He demonstrated the mechanical adaptation of bone tissue experimental animal models of overloaded or disuse bone. He trained more than 200 scientists from across the world. He always thought about young scientists, then established the Alice Jee Memorial Young Investigator Awards which supported numerous students. He was a recipient of the ASBMR Gideon A. Rodan Excellence in Mentorship Award (2003).

The Sun Valley International Hard Tissue Workshop

Between 1965 and 2003, the period when W.S.S. Jee was the Organizer and Director, the Sun Valley Workshops were the genesis of such concepts and techniques as dynamic histomorphometry, the quantum concept of bone turnover, the BMU as the functional unit in bone, coupling between bone resorption and bone formation, strain-feedback mechanisms and the mechanostat, mechanisms of mechanical signal transduction, osteocyte biology, and the role of microcracks both as contributors to skeletal fragility and as a stimulus for repair of bone tissue. Bone Morphogenic Protein was one of the topics in the early '70s. These concepts and approaches first discussed at the workshop lay the foundation for developing and understanding the mechanisms for novel treatment regimes for osteoporosis, including early work on anabolic treatments using intermittently administered parathyroid hormone (now called teriparatide) and combination treatments involving more than one pharmaceutical modality. By the late 1990's, such discussions had evolved from the tissue level to include cellular and molecular events related to mechanisms of adaptation and the pathophysiology of the skeleton. Concepts first presented and critiqued at these Workshops subsequently have been incorporated into nearly every discipline that currently works on skeletal problems. Since 2003 through 2017 when D.B. Burr was the Organizer and Director, the SV Workshop has expanded more broadly to include holistically all musculoskeletal tissues and their involvement in health and disease, and now partners with the Orthopaedic Research Society. Current topics address cartilage and osteoarthritis, tendon and ligament biology and repair, epigenetics and rare bone diseases, among others. Historically, the Workshop was key to developing and training investigators in the use of novel methodologies to study bone; it continues to concentrate on modern methodologies and how these can be used to understand normal physiology and dysfunction of the musculoskeletal tissues. The Workshop began as a training program for dental students in research and has always focused on younger investigators. These programs have been expanded by incorporating additional Young Investigator Awards funded by the ASBMR and by Indiana University, providing Career Development Workshops on a variety of topics during some afternoon sessions, and establishing a Blue Ribbon Award program for exceptional student and Fellow posters. As such, the ORS Musculoskeletal Biology Workshop continues to be one of the premier small workshops not only for studying the musculoskeletal tissues, but also for training the new generation of musculoskeletal investigators.

Preface

This book provides basic and current knowledge of bone tissue in health and osteoporotic fracture, together with systemic skeletal disorders, to students and trainees of multi-professionals in health and social care fields who care for the elderly. The intention in each chapter is explained in the executive summary. A reader could start to read from any chapter, such as the treatment of osteoporosis by a drug, then return to a chapter on the basic science of remodeling and/or modeling. This way your knowledge is deepened from the level of a practitioner or a junior staff member busy in daily practice to the level of a young researcher curious to know how these concepts developed.

Would you allow us, the authors, to ask you to consider the meaning of two key words: remodeling and modeling of bone? Even in the community of bone and mineral research, some researchers use the very same word, "remodeling," to apply to very different concepts that have very different meanings. Remodeling has a very specific definition: it is a sequential process in which activation–resorption–formation occur at a single site. Recently, an additional step was proposed, activation–resorption–reversal/resorption–formation, which several chapters will discuss. This does not apply to modeling (in which only activation and either resorption or formation occur at a single site) nor does it apply to "lacunar remodeling," which does not involve osteoclasts or osteoblasts at all. Terminology is important as it shapes our understanding of adaptive processes. One goal of the current book is to frame musculoskeletal modeling and remodeling in the proper context so that professionals can communicate clearly and accurately across disciplines.

Osteoporosis is a disorder of imbalance of bone resorption and formation in remodeling, called BMU-based remodeling (basic multicellular units-based remodeling). Investigation into the dynamics of bone turnover was started in the early 1960s by Harold M. Frost at Henry Ford Hospital in Detroit, who established a histological method to quantify bone changes using tetracycline as a time marker. One editor (HET) who was in training under him witnessed the dawn of bone histomorphometry.

The concepts surrounding BMU-based bone biology were developed at the International Hard Tissue Workshops, held in Sun Valley, Idaho nearly every summer since 1965 (now called the ORS Musculoskeletal Biology Workshop). The founder and organizer was Webster SS Jee of Utah. This Workshop was a kind of think tank for bone histomorphometry and bone biology, where young researchers

were most welcome and spent much time in discussion. One editor (NY) worked in Jee's laboratory as a research fellow. Dr. Jee was the organizer until 2003. A subsequent organizer of the international workshop from 2004 to 2017 is one of editors (DBB) of this book.

In the late 1990s, after the introduction by Frost of the Mechanostat concept, discussions at the Workshop began to consider how mechanical forces regulate growth, modeling, and remodeling. These discussions helped to develop the concepts surrounding mechanotransduction—how mechanical signals are translated into cellular responses. Subsequent Workshops focused on many of the topics addressed in this book: fracture healing, metabolic bone diseases (in addition to osteoporosis), the regulation of skeletal physiology, and the roles of biomechanics in skeletal development and disorders. In more recent years, the Workshop has expanded to consider important issues of musculoskeletal health and disease beyond those of just bone—issues related to cartilage (the arthritides), muscle (sarcopenia), and tendons/ligaments (healing)—and the appropriate animal models to study them. This takes a more holistic approach to the musculoskeletal apparatus as an integrated system in which there is crosstalk among the various tissues. So, although this book focuses primarily on bone, the chapters should be read and understood in the context of this more holistic musculoskeletal framework.

Niigata, Japan — Hideaki E. Takahashi
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Executive Summary

This summary will briefly introduce the contents of the book including a broad treatment of existing basic and clinical knowledge and new information about how to assess and treat osteoporotic fractures. This book consists of eight parts and 38 chapters, which are contributed by active researchers and experienced clinicians.

Part I: Basic Mechanisms of Skeletal Physiology and Repair
The understanding of the pathophysiology of osteoporosis, and therefore the basis for its prevention and treatment, must start with an understanding of basic bone biology at the organ, tissue, cell, and molecular levels. In the chapter "Cellular and Molecular Biology in Bone Remodeling", Donahue and colleagues provides an overview of bone remodeling and its cellular and molecular basis. Cells and molecular signaling are highly regulated by the mechanical environment, and in the chapter 2 "Bone Tissue and Its Mechanical Regulation of Remodeling", Robling reviews the mechanisms by which this occurs. Changes that occur during aging contribute to bone fragility even in those who are not, by definition, osteoporotic. In the chapter 3 "Effects of Aging on Skeletal Fragility", Burr reviews the changes that occur during aging and how they contribute to bone fragility and potentially increase the risk for osteoporotic fractures.

Part II: Methods of Assessment: Bone Morphometry of Remodeling and Modeling
In this section, the relationship between bone formation and resorption in bone renewal is described at the tissue level. In the chapter "Histomorphometric Assessment of Remodeling and Modeling-Based Mineral Apposition", Ma provides basic knowledge of bone histomorphometry. In chapter the "Bone Minimodeling, Modeling-Based Bone Formation in Trabecular, Endocortical and Periosteal Bone", Takahashi, et al. review minimodeling, i.e., modeling at the microscopic level. In the chapter "Mechanism Reversing Bone Resorption to Formation During Bone Remodeling", Delaisse, et al. describe the role of canopy and reversal cells in remodeling. In the chapter "Significance of Reversal-Resorption Phase in Bone Loss", Andersen, et al. describe the reversal-resorption phase in cortical remodeling. In the chapter "Bone Remodeling and Modeling: Therapeutic Targets for the Treatment of Osteoporosis", Langdahl provides knowledge of

remodeling and modeling in osteoporotic treatment. In the chapter "Three-Dimensional Microstructural Measurement for Predicting the Risk of Osteoporotic Fracture", Nango, et al. describe how three-dimensional microstructural measurements can help to predict the risk of osteoporotic fracture.

Part III: Radiological, Biochemical, and Clinical Methods of Assessment
Osteoporosis generally is detected through some standard imaging methods, and through the biochemical measurement of markers for bone formation and resorption. In the chapter "Clinical Diagnostic Tools of Osteoporosis: Vertebral Fracture Assessment and Measurement of Bone Mineral Density (BMD)", Ito describes the use of DXA and semi-quantitative methods for analysis of the lateral thoracic spine. In the chapter "Assessment of Osteoporosis by QCT, HR-pQCT, and MRI", Chiba, et al. describe high-resolution peripheral quantitative computed tomography (HR-pQCT). In the chapter "Bone Turnover Markers", Ichimura reviews bone turnover markers of both bone formation and resorption.

Part IV: Microdamage and Bone Fractures
Part of the pathophysiological basis for some osteoporotic fractures is the accumulation and failure to adequately repair microdamage and larger focal porosities in bone. In the chapter "The Role of Microdamage in Bone Mechanics and Osteoporotic Fractures", Allen reviews the basic science of microdamage initiation, crack growth, and repair and how it can contribute to, or prevent, fracture. In the chapter "Focal Osteoporosis and Its Role in Subcapital Hip Fracture", Poole, et al. identify regional focal changes in the hip associated with aging and osteoporosis and provide some sophisticated ways of using computerized tomography and histomorphometry to identify these changes and evaluate their mechanical significance. In some cases, full osteoporotic fractures, or impending and developing fractures do not heal properly. In the chapter "Fracture Healing and Cause of Non-union", Mori discusses the reasons for this, and the appropriate management of non-unions. In chapter "Disturbance of Osteonal Remodeling in Atypical Femoral Fracture: A Short Review of Pathogenesis and a Case Report: Histomorphometric Analysis of Fracture Site", Takahashi et al. describe histomorphometric evidence related to the pathogenesis of atypical femoral fractures that often are associated with bisphosphonate treatments for osteoporosis.

Part V: Metabolic and Systemic Skeletal Disorders
Systemic diseases may cause unusual skeletal disorders. Neither DXA scans nor serum bone metabolic markers can reveal the pathogenesis of bony lesions. Bone biopsy for bone histomorphometry in the clinical setting is a valuable and well-established procedure to study the etiology, pathogenesis, and therapeutic approaches to skeletal lesions. In this section, we identify the structural and kinetic features of cortical and cancellous bone and the alteration of bone remodeling by Vitamin D deficiency in the chapter "Mineralization Impairment Due to Vitamin D Deficiency in Bone Histomorphometry" (Yamamoto et al.), diabetes mellitus in the chapter "Diabetes and Bone" (Yamada et al.), chronic kidney disease (CKD) in the

chapter "Bone Lesions in Patients with Chronic Kidney Disease: A Focus on Special Attention on Tetracycline Labeling-Dependent Bone Histomorphometry" (Kazama), and other miscellaneous diseases (hepatic C-associated osteosclerosis, IgG4-related disease, and Ehlers–Danlos syndrome) in the chapter "Bone Histomorphometry in Miscellaneous Metabolic Diseases: Hepatic C-Associated Osteosclerosis, IgG4-Related Disease, and Ehlers–Danlos Syndrome" (Yamamoto et al.). This provides diagnostic clues in unclear bone disorders. All clinicians should consider bone biopsy when met with unusual fractures or unknown calcium metabolism in clinical practice.

Part VI: Effects of Osteoporosis Drugs

There are now many options for pharmaceutical treatment of osteoporosis. Some of these prevent bone remodeling and thereby slow the loss of bone. Other treatments are anabolic and can re-establish bone mass to reduce the risk of fracture. Each of these has different characteristics, potencies, indications for use, and potential side effects, and may be used for different populations of osteoporotic individuals. Chapters "Effects of Osteoporosis Drugs: Morphological Assessment and Adverse Events" (Bisphosphonates, Kimmel), "Denosumab in the Treatment of Postmenopausal Women with Osteoporosis: Fracture Outcomes, BMD, and Morphological Assessment" (Denosumab, Wagman et al.), "Selective Estrogen Receptor Modulators" (SERMs, Burr and Phipps) take up the issue of the agents that suppress bone remodeling and reduce bone loss. Chapters "Teriparatide" (Teriparatide, Marin and Ma), "Effects of Once-Weekly Teriparatide Treatment on Trabecular Bone Microdamage Accumulation and Cortical Structure in the Lumbar Vertebrae of Ovariectomized Cynomolgus Monkeys" (weekly administration of Teriparatide, Mashiba et al.), and "Romosozumab Treatment for Osteoporosis: Pharmacological Stimulation of Mechanical Strain-Related Bone Modeling" (Romosozumab, Sugiyama) consider the "anabolics" that can add to bone mass by adjusting the balance of bone formation and bone resorption. In the chapter "Morphological Assessment of the Biological Effects of Eldecalcitol", Hasegawa et al. describe minimodeling by Vitamin D [Eldecalcitol]. Sometimes these drugs are used clinically in combination. In the chapter "Effects of the Drug Treatment for Osteoporosis in Clinical Settings, Monotherapy or Concurrent Therapy", Mori describes the effects of monotherapy or concurrent therapy for the treatment of osteoporosis in clinical settings. In the chapter "Current Treatment of Osteoporosis and Future Prospects", Compston provides an overview of all these treatments and their indications.

Part Vll: Various Aspects of Osteoporosis Treatment

One risk contributing to osteoporotic fracture, particularly hip fractures, is muscle weakness or sarcopenia that increases postural instability that may contribute to falling. Whole body vibration exercises can improve muscle mass and strength, as well as neuromuscular performance. In the chapter "Whole Body Vibration as an Exercise Modality to Prevent Sarcopenia and Osteoporosis", Rittweger reviews the evidence for this as a viable therapeutic option in geriatric and rehabilitation

medicine. Cost-effectiveness of drugs is important in maintaining treatment for any disease. In the chapter "Cost-Effectiveness of Osteoporosis Treatment", Moriwaki provides such an analysis for osteoporosis treatment.

Part VIII: Operative Treatment of Osteoporotic Fractures

Operative treatment is indispensable in handling osteoporotic fractures and spinal deformities. Everyone who cares for osteoporotic patients should know what conditions require surgery and what surgeons can do. Preoperative planning should define the desired primary outcome to postoperatively re-establish the preoperative level and quality of activities of daily living. Frequent life-threatening osteoporotic fractures and their complications occur in the hip and spine. In the chapter "Pre- and Perioperative Management of Hip Fracture", Shigemoto et al. describe the pre- and perioperative management of hip fractures. In the chapter "Surgical Treatment of Femoral Neck Fracture", Imai, et al. describe operative treatment of femoral neck fractures, and in the chapter "Surgical Treatment of Intertrochanteric Femur Fracture", Watanabe describes that of intertrochanteric fractures in Japan. In the chapter "Operative Treatment of Hip Fractures in Osteoporotic Patients", Hannon and Jacobs describe management of hip fractures in the United States. In the chapter "Operative Treatment of Osteoporotic Spine", Yamazaki discusses surgery for the osteoporotic spine. In the chapter "Post-surgical Rehabilitation and Mortality After Proximal Hip Fracture Surgery", Kimura describes and emphasizes the importance of rehabilitation after surgery in Japan. Postoperative management for hip fractures is different depending upon health and social care systems. In the chapter "National System and Comments on the Holistic Elements of Care of the Elderly with Overview of Hip Fracture Research and Service", Dixon, et al. describe contemporary hip fracture care in the United Kingdom.

In combination, these chapters provide an overall view of the etiology and pathogenesis of osteoporosis, and a guide to the therapeutic and rehabilitative approaches to bone changes that occur with aging and with osteoporosis.

Editors

Contents

Part I

Basic Mechanisms of Skeletal Physiology and Repair

Cellular and Molecular Biology in Bone Remodeling

Rachel C. DeNapoli, Evan G. Buettmann, and Henry J. Donahue

Keywords

Osteoblast · Osteoclast · Osteocytes · Cancellous · Cortical · Haversian · Basic multicellular unit · Perilacunar · Bone remodeling

1 Clinical Rationale

1.1 Introduction

Bone is a dynamic mixture of cells, collagen and hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). In order to maintain its structural integrity and provide mineral homeostasis bone is constantly remodeled throughout postnatal life [1]. Normal bone remodeling occurs in either bone type (cortical or cancellous) by the coordinated action of bone formation by osteoblasts and bone resorption by osteoclasts. In normal physiological conditions, bone formation and resorption are nearly equal and there is no net change in bone mass. However, under different levels of exercise or pathological conditions bone mass can change due to an imbalance in overall remodeling. When bone mass decreases, skeletal fragility can result, which subsequently increases a patient's risk of fracture. The increased risk of fracture is only partially explained by a reduction in bone mass and is dictated by other parameters such as bone structure and material

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quality [2]. Nonetheless, increased skeletal fragility is found in patients with bone remodeling disorders such as osteoporosis and other pathologies [3, 4].

1.2 Bone Remodeling Disorders

Osteoporosis is a disease characterized by low bone mass, compromised bone strength, deterioration of bone tissue, and disrupted bone architecture. It has a widespread incidence affecting 1 in 2 women and 1 in 5 men over the age of 50 [5]. The clinical definition of osteoporosis, defined by the World Health Organization (WHO), is bone mineral density (BMD) at the hip or lumbar spine of a patient being less than or equal to 2.5 standard deviations below the young healthy reference population (30 years old) mean BMD (called a T-score) [6]. Osteopenia is a disease in which bone density is below average (T-score between −1 and −2.5), though not as severe as osteoporosis [7]. Some causes of low bone mass are estrogen deficiency, as seen in postmenopausal women, glucocorticoids, disuse, and diabetes/obesity [6]. Treatments to alleviate symptoms of osteoporosis include lifestyle changes, such as cessation of smoking, reduction of alcohol use, and increased physical activity. Vitamin D and calcium supplements may also improve bone health but can have unintended drawbacks seen in other organ systems, such as calcium buildup in the cardiovascular system [8]. The most effective pharmaceutical therapies for osteoporosis treatment are anti-resorption drugs, such as bisphosphonates (Chapter "Effects of Osteoporosis Drugs–Morphological Assessment and Adverse Events") and Denosumab (Chapter "Denosumab in the Treatment of Postmenopausal Women with Osteoporosis: Fracture Outcomes, BMD, and Morphological Assessment"), that minimize bone resorption [8–10].

2 Bone Cells and Associated Functions (Fig. 1)

Osteoclasts are multinucleated cells, derived from monocytes of the hematopoietic lineage that function to resorb bone. The differentiation of monocyte lineage cells into mature osteoclasts is dependent on receptor activator of NF-kB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [11]. M-CSF binds to its receptor (c-Fms) on osteoclast precursors and mature cells to stimulate their proliferation and survival [11]. However, RANKL, which is expressed by both osteoblasts and osteocytes, is the primary osteoclast differentiation factor [11]. RANKL binds to its receptor, RANK, present on osteoclasts, to induce transcription factors and enzymes that promote bone resorption. Osteoprotegerin (OPG), an endogenous antagonist to RANKL, inhibits RANKL binding to RANK by acting as a decoy receptor [8, 12]. OPG is secreted by osteoblast lineage cells to aid in the tight regulation of osteoclastogenesis [12, 13]. Osteoclasts are able to resorb bone due to their motile cytoskeleton, adhesion molecules, and a ruffled border at the bone surface [8, 14]. These qualities of osteoclasts allow for their attachment to bone, largely via αVβ3 integrins, and the creation of a sealed-off microenvironment between the osteoclast ruffled border and the bone surface. At the ruffled border active carbonic anhydrase

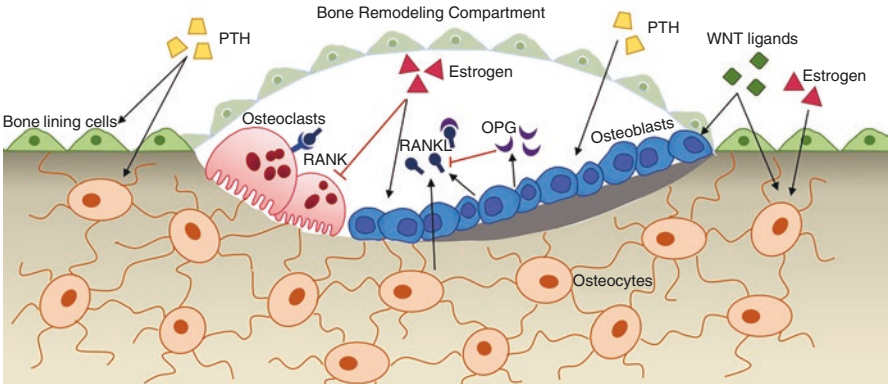

Fig. 1 Overview of cellular and molecular mediators of bone remodeling. The Bone Remodeling Compartment (BRC) is a specialized environment where bone remodeling occurs through osteoclasts resorbing old or damaged bone tissue, and osteoblasts forming new bone matrix. Bone remodeling is tightly regulated and is driven by local osteocytic factors such as RANKL, OPG, and WNT ligands or via endocrine signaling by estrogen and PTH. Specifically, estrogen acts on osteoblasts and osteocytes to promote bone formation, while inhibiting osteoclastic bone resorption. PTH has pleiotropic effects on bone. It acts on the osteoblasts, osteocytes, and bone lining cells to directly promote bone formation or to cause osteoblasts and osteocytes to release RANKL. RANKL then binds to RANK receptors on osteoclasts, to promote osteoclastogenesis. However, osteoblasts and osteocytes release a decoy receptor, OPG, that tightly regulates osteoclastogenesis by inhibiting RANKL-RANK binding. WNT ligands, part of the β-catenin canonical signaling pathway, play a major role in bone remodeling by acting on osteoblasts and osteocytes to promote osteoblastogenesis and indirectly control osteoclastogenesis. Abbreviations: receptor activator of NF-κB ligand, OPG, osteoprotegerin, PTH, parathyroid hormone

converts CO_2 and H_2O to bicarbonate (HCO3-) and protons (H+) that are secreted into the resorption compartment creating an acidic environment. This acidic environment allows for activation of osteoclast specific matrix metalloproteinases, including tartrate resistant acid phosphatase (TRAP), and the collagenase cathepsin K, which facilitates breakdown of the extracellular matrix and resorption of bone matrix [8, 15, 16]. Cathepsin K aids in removing poor quality bone where microcracks have accumulated and hole-like lacunae have formed [8]. TRAP is highly expressed by mature osteoclasts during bone resorption and is critical for skeletal development [14, 17]. Another highly expressed enzyme produced by mature osteoclasts is Src kinase [8]. Src kinase's main role is to mediate multiple pathways that regulate osteoclast activity, but not number, such as formation of a ruffled border critical for bone resorption. Without the presence of Src kinase there will be an increase in osteoblastic bone formation, but no effect on overall osteoclast number.

Osteoblasts, derived from mesenchymal stem cells, are primarily responsible for the synthesis of bone extracellular matrix. This process, often referred to as osteogenesis, is crucial for the proper development and maintenace of bone. In adult skeletons, osteoblasts are recruited to regenerate, or remodel, areas of bone with depleted matrix or defects [8, 18]. To synthesize bone at sites of resorption, osteoblasts secrete bone matrix proteins, such as collagen type 1 (Col1) and

noncollagenous proteins such as osteocalcin (OCN) and osteopontin (OPN). Through osteoblast derived alkaline phosphatase (ALP) [8, 19] the synthesized bone extracellular matrix (called osteoid) undergoes mineralization to form hydroxyapatite [18–20]. Osteoblast differentiation is controlled by two well-studied transcription factors: Runt-related transcription factor 2 (RUNX2) and Osterix (Osx). RUNX2 is an essential bone-specific transcription factor that causes the upregulation of osteoblast differentiation marker genes and induces osteogenesis [8, 21]. Osx is located downstream of RUNX2 and is required for osteoblast maturation and bone mineralization [18, 21, 22]. Osteoblast growth and differentiation are also mediated by different classical signaling pathways such as transforming growth factor-beta (TGF-β), bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and the WNT/ β -catenin pathway [23]. Furthermore, osteoblasts are sensitive to mechanical stimuli resulting from mechanical loading [8, 18, 20].

Osteocytes are the most abundant cell type in bone and comprise about 90–95% of all the cells in bone [24]. They are terminally differentiated, post-mitotic osteoblasts that have become embedded in mineralized bone matrix. The osteocyte has two major components: (1) a central cell body in a bone cavity called a lacuna (15–20 microns in humans) and (2) small dendritic projections (50–100 per cell) [25] coming off the cell body that protrude through microscopic (50–300 nm) [26] channels called canaliculi. This vast network of lacunae and canaliculi make up the lacunar-canalicular system of bone, which is thought to serve as a biochemical transport system between osteocytes, vascular channels, and bone surfaces as well as a mechanical amplification system. Through these expansive networks, osteocytes can connect and transport small molecules to neighboring bone cells via gap junctions (see section "Important Molecules in Bone Remodeling"). Due to these features, osteocytes have been implicated as the key mechanosensitive and endocrine regulated cell in bone that regulates bone mass. Osteocytes express higher levels of key bone matrix and phosphate regulatory molecules, including osteocalcin (OCN, dentin-matrix protein 1 (DMP1), phosphate-regulating neutral endopeptidase (PHEX), matrix extracellular, phosphoglycoproteine (MEPE) and fibroblast growth factor 23 (FGF23), than osteoblasts [27]. They also express molecules that directly inhibit osteoblast formation and activity, such as dickkopf-related protein 1 (Dkk1) and sclerostin, and regulate osteoclast formation via RANKL and its decoy receptor OPG. Osteocytes can live the entire lifetime of the host (mean half-life 25 years) [28] or undergo apoptosis (i.e., programmed cell death) due to various environmental stimuli such as bone microdamage (linear microcracks), estrogen deficiency, unloading, or glucocorticoid use [29]. It was first shown by Cardoso et al. that osteocyte apoptosis, which occurs in microdamaged regions of the bone following fatigue loading (which results in microcracks), is a key event necessary for targeted intracortical remodeling [30]. Subsequent *in vitro* and *in vivo* work has suggested that apoptotic osteocytes near fatigue damage microcracks in bone (≤300 microns) do not secrete any signals and therefore this response is

fairly targeted to the damaged bone region. This same effect is apparent in estrogen withdrawal after ovariectomy, where osteocyte apoptosis is upregulated 4–7 times in the posterior diaphyseal cortex, resulting in activation of endosteal resorption [33]. Estrogen signaling is necessary for continued mitigation of mitogen-activated protein kinases (MAPKs) activation, which neutralizes reactive oxygen species (ROS) in osteocytes thereby preventing apoptosis [29].

2.1 Bone Types and Haversian System

Structurally, bone is composed of two distinct types, cancellous and cortical. ***Cancellous bone*** is found at the end of long bones (epiphysis/metaphysis) or in flat bones, such as the pelvis, clavicle and cranium, and is made up of highly arranged trabecular struts. These trabecular struts, in humans, can be dominated by a rod- or plate-like architecture, are 150–300 microns thick and interspaced every 0.5 to 1.5 mm [34, 35]. Therefore, cancellous bone has a large surface area to volume ratio (porosity of 0.5–0.95) and its remodeling serves a primary metabolic function in the body. Cancellous bone remodeling starts at the surface of the trabeculae and usually takes about 200 days to complete [36]. In contrast, ***Cortical bone***, which is denser and more compact, makes up the outer covering of all bone and is sometimes referred to as compact bone. Cortical bone's structure and a usually lower rate of turnover enable it to serve a primarily load-bearing function. Human cortical bone is initially formed and made up of discrete units called osteons that make up the Haversian system of bone. These osteons are cylindrical in nature and consist of blood vessels and nerves at their center (Haversian canal) surrounded by rings of concentric layers of compact bone called lamellae. Interspersed between these layers of lamellar bone are osteocytes and their lacunar-canalicular system. Osteons are typically 200 μm in diameter and 3 mm in length [37]. Both cancellous and osteonal remodeling occurs by the stochastic and coordinated action of multiple cell types, termed basic multicellular units (BMU's), that remodels bone [38, 39].

2.2 "Basic Multicellular Unit" BMU-Based Remodeling

The replacement of old osteons in cortical bone or trabecular struts to form secondary (i.e. new) osteons or new trabeculae, respectively, occurs by the coordinated action of a group of bone cells termed the "Basic Multicellular Unit" (BMU), which creates a structural feature of bone tissue called the "Bone Remodeling Unit" (BRU) [40]. These processes occur in a specialized environment, that is enclosed by canopy cells and is vascularized and innervated, called the "Bone Remodeling Compartment" (BRC) [41] (see Chapter "Cellular and Molecular Biology in Bone Remodeling"; Fig. 1 and Chapter "Mechanism Reversing Bone Resorption to Formation During Bone Remodeling"). Bone remodeling in total occurs across

several discrete phases named in order of their occurrence; Activation-Resorption/Reversal-Formation (A-R-F) (see Chapter "Bone Remodeling and Modeling: Therapeutic Targets for the Treatment of Osteoporosis"). In the ***activation phase***, hormonal (PTH) or mechanical remodeling signals (RANKL, microdamage) sensed by the osteocyte and osteoblasts, signal to pre-osteoclasts to undergo osteoclast formation and resorptive activity [42–44]. This activation phase is quick and lasts 1–3 days. Once osteoclasts have formed, the resorption phase begins with the osteoclasts forming an ellipsoidal "cutting cone" in cortical bone or Howship's lacunae in cancellous bone [45]. The osteoclasts begin to resorb bone along the anatomical axis of the osteon or trabeculae at a rate of 20–40 μm per day for about 3 weeks [46], leaving behind demineralized and partially digested bone matrix. Following osteoclast-mediated resorption, a ***reversal stage*** begins that initiates bone formation (see Chapter "Significance of Reversal Resorption Phase in Bone Loss"). Although the cell type responsible for initiating bone formation is contested [1, 47–49], it is generally accepted that this specialized cell prepares the bone surface and potentially secretes coupling factors to promote osteoblast formation and activation. In the last phase of BMU based bone remodeling, the ***formation phase***, osteoblasts deposit a new unmineralized bone matrix, called osteoid, into the prepared resorption spaces. This osteoid is later mineralized with the help of specialized metalloenzymes, such as alkaline phosphatase, from the osteoblast [50, 51]. These osteoblasts can then either become entrapped in minerals to form osteocytes, undergo apoptosis, or become quiescent to form lining cells that cover the new bone surface to aid in the next remodeling cascade [52, 53].

2.3 Perilacunar Remodeling

The lacunar-canalicular system is vast. In humans, it makes up an area of bone nearly 215 m^2 [2] and therefore represents a large reservoir of available minerals and bioactive molecules. Osteocytic osteolysis, or the newer term, perilacunar remodeling (also called perilacunar turnover to distinguish it from bone remodeling involving the BMU which requires both osteoclasts and osteoblasts), is now recognized as a distinct form of bone turnover that is carried out directly by the osteocyte. Typically, perilacunar remodeling is associated with conditions that place rapid demands on the skeleton, such as lactation, calcium restriction, and space flight. In fact, experiments have shown that at any one time 15–20% of osteocytes are associated with new bone-forming surfaces and can produce the same enzymes used by osteoclasts to resorb bone including matrix metalloproteases (MMPs), proton pumps, carbonic anhydrase, and cathepsin K [24, 54, 55]. More recent evidence has shown that perilacunar remodeling is coordinated via TGFB-β and PTH receptor signaling in osteocytes as well as the downstream transcriptional regulators Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) [54, 56, 57]. More importantly, these same studies show that perilacunar remodeling has a direct effect on the local bone matrix quality and therefore can directly influence fracture resistance.

3 Important Molecules in Bone Remodeling

3.1 Local (Paracrine and Autocrine)

Receptor activator of nuclear factor-kappa-β ligand (RANKL), its receptor RANK and Osteoprotegerin (OPG)—RANKL is expressed in the local bone microenvironment by osteoblast lineage cells (osteoblasts and osteocytes) and signals to its receptor RANK on osteoclastic precursor cells to control their fusion, survival, and differentiation into mature osteoclasts [58]. RANKL is highly upregulated in bone cells, especially osteocytes exposed to PTH, after bone damage, and disuse [59]. People with mutations in the RANKL gene (TNFSF11) demonstrate osteopetrosis or excessively brittle bone due to hypermineralization [60]. On the other hand, OPG is a decoy receptor for RANKL that is expressed by osteoblast lineage cells and blocks osteoclastogenesis through competitive inhibition of RANKL-RANK binding [61]. OPG is upregulated due to bone loading, estrogen, and transforming growth factor β (TGF-β) [62]. Therefore, RANKL/OPG pathways play a key role in coordinating bone resorption by various local and systemic regulators.

WNT/β-Catenin Signaling and Sclerostin—The WNT/β-catenin signaling pathway has emerged as a major pathway controlling bone remodeling. In canonical WNT signaling, WNT ligands (19 distinct proteins in vertebrates) bind to the frizzled receptor with co-activators LRP4/5/6. This results in β-catenin stabilization, nuclear translocation and binding to TCF/LEF in the cell nucleus. This stabilization increases transcriptional activation of genes that increase osteocyte/osteoblast proliferation, viability, and bone formation while simultaneously decreasing bone resorption via decreased RANKL/OPG signaling [63, 64]. Therefore, modulating WNT/β-catenin has become a key target to improve bone mass and quality by increasing bone formation while downregulating resorption. One key approach used to modulate WNT/β-Catenin signaling is by inhibiting sclerostin, the product of the SOST gene and a WNT/β-Catenin antagonist that binds LRP5/6. Sclerostin is primarily produced by osteocytes, is regulated by loading, and mutations in the gene lead to high bone mass disorders such as Sclerosteosis or Van Buchem's disease [65–68].

Gap Junctional Intercellular Communication (GJIC)—Gap junctions are membrane-spanning protein channels that allow for the passage of small molecules such as ATP, calcium, prostaglandin, and microRNAs between bone cells [69]. The predominate gap junction protein in bone is connexin 43 (Cx43), which is encoded by the GJA1 gene and highly expressed by osteoblast lineage cells, especially osteocytes. It is found at the connections between osteocytes and other bone cells and is necessary for osteocytic regulation of osteoblasts via mechanical stimulation [70]. Mutations in the GJA1 gene in humans cause oculodentodigital dysplasia and are associated with high turnover osteopenia and increased intracortical porosity [71–73]. This is likely because Cx43 is necessary for normal osteoblast lineage cell differentiation, development, and function. Cx43 has also been shown to play a large role in skeletal homeostasis and skeletal adaptation to mechanical loading. For example, loss of Cx43 in osteoblast lineage cells (osteoblasts and osteocytes) attenuates bone loss seen with unloading [74, 75]. Interestingly, the same conditional

deletion of Cx43 leads to greater bone formation with skeletal loading [76, 77]. These studies and recent reviews suggest that these beneficial skeletal results are due to Cx43's regulation of osteocyte apoptosis and specific factors such as PGE2, sclerostin, and RANKL/OPG, respectively, that are critical for normal bone remodeling [74, 78–81].

3.2 Systemic (Endocrine)

Parathyroid Hormone (PTH) is an important hormone for maintaining bone homeostasis. It is secreted by the parathyroid glands and plays a key role in coordinating serum calcium and phosphate homeostasis [82]. Specifically, PTH works by binding to its receptor, which is found on all cells of the osteoblast lineage (i.e., bone lining cells, osteoblasts, osteocytes) [83]. PTH receptor activation increases bone formation by converting bone lining cells to active osteoblasts, decreasing osteoblast apoptosis and promoting osteoblastic differentiation by acting as an upstream regulator of RUNX2 [43, 84]. Furthermore, PTH receptor activation of osteocytes increases RANKL mediated osteoclastogenesis and decreases sclerostin expression [85, 86]. However, the effect of PTH on bone is time-dependent. While a constant, elevated level of PTH stimulates bone resorption, an intermittent dose is anabolic and promotes bone formation [18]. Teriparatide, a recombinant form of active PTH, is the oldest and most commonly used bone anabolic drug to treat osteoporosis [87] (see Chapter "Teriparatide").

Estrogen (17β-estradiol) is another important hormone for bone, particularly for women. 17β-estradiol, the most common form of estrogen, has direct effects on bone cells by binding to the estrogen receptors alpha and or beta (ERα and ERβ), which are found on osteoblasts, osteoclasts, and osteocytes [88]. ERα and ERβ activation directly promotes osteocyte and osteoblast function, inhibits their apoptosis, and inhibits osteoclast activation and function [88–90]. All of these estrogen functions work to prevent bone loss and maintain skeletal mineralization. However, postmenopausal women experience a decline in ovarian estradiol levels, which leads to decreased BMD levels [89, 91]. Men also experience a decline of estrogen levels with age, but not to the same extent as women [89]. These decreased serum estradiol levels can be predictive of bone fracture and development of osteoporosis in both men and women [89, 91].

Other systemic factors, including but not limited to **Calcitonin**, **FGF23, and Insulin** are also important for bone remodeling. Calcitonin is released by thyroid cells and binds to osteoclasts to inhibit bone resorption [92]. FGF23 is produced by mature osteocytes to help the kidneys regulate serum phosphorous levels and maintain mineral homeostasis [93–95]. Insulin is an important hormone in both energy and bone metabolism [96]. Insulin is recruited to bone through the osteoblastic release of osteocalcin, which signals to pancreatic β-cells to release insulin [97]. Insulin acts directly on bone cells by decreasing OPG production from osteoblasts, thereby increasing RANKL concentrations that can activate osteoclasts [97].

Biomarkers and Assays of Bone Remodeling—To determine the status of bone turnover, serum biochemical markers, and bone biopsies are used clinically (see Chapter "Metabolic Boneturnover Markers"). The iliac crest is a common biopsy site used to simultaneously observe cortical and trabecular bone mineralization and cellular features histologically [98, 99]. Usually, iliac crest biopsies are taken after systemic administration of a bone chelating agent, such as tetracycline, which can be analyzed histologically to assess rates of bone turnover [98–100] (see Chapter "Histomorphometric Assessment of Remodeling and Modeling-Based Bone Formation "). A noninvasive assay to evaluate bone turnover involves quantifying biochemical markers in blood serum following fasting. Common serum bone formation markers are osteocalcin (OCN) and procollagen type I N-terminal propeptide (P1NP). Common serum bone resorption markers are C-terminal telopeptide (CTX), N-terminal telopeptide (NTX), and TRAP5b [98, 101]. Other serum biochemical markers assessed include PTH, insulin-like growth factor I (IGF-I) (an anabolic hormone for bone), and vitamin D [96, 101].

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