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Andy H. Choi · Sian Yik Lim
Editors

Pharmacological Interventions for Osteoporosis

Springer

Tissue Repair and Reconstruction

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Preface

Preventing osteoporosis and its associated fractures is regarded as crucial in maintaining the independence, health, and quality of life of the elderly because of the maleficent effects of osteoporosis. Age-related bone loss is asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that take place. Osteoporosis results in skeletal fragility along with a heightened risk of fracture caused by a change in bone remodeling. It has been accepted that the principle behind the bone remodeling sequence is to sustain the integrity of the skeleton. This is accomplished through the collaborative efforts of osteoclasts (responsible for bone resorption) and osteoblasts (responsible for bone formation). Bone resorption and bone formation are balanced in homeostatic equilibrium. On a cellular level, simultaneous mechanical and biological actions play a governing role in the delicate equilibrium between bone growth, formation, and resorption. In osteoporosis, however, the quantity of resorbed bone by osteoclasts exceeds the amount of bone formed by osteoblasts resulting in a reduction in bone strength and damage to the skeletal architecture.

The purposes of intervention are to avoid bone loss in patients diagnosed with osteoporosis as well as in individuals at risk of osteoporosis. Treatments may be targeted at maintaining bone mass or repairing skeletal deficits. The objectives of interventions and treatment focus are identical, that is to decrease the chance of osteoporotic fractures by maximizing skeletal strength. Changes in lifestyle are helpful but patients that have a high risk of fracture will often also require pharmacological interventions. A number of biological studies have revealed the mechanisms governing bone remodeling and consequently resulted in the discovery of new pharmacological targets that could aid in enhancing bone health in patients diagnosed with osteoporosis. The medications used in the treatment of osteoporosis can be categorized into either primarily anabolic or anti-resorptive. Anabolic pharmaceutical agents are responsible for promoting new bone formation, whereas anti-resorptive pharmaceutical agents are responsible for the prevention of bone resorption. Due to their capacity to selectively restrain the activity of osteoclast and ultimately slow down bone resorption, bisphosphonate therapy has become the primary clinical intervention for postmenopausal osteoporosis for the past two decades. On the other hand, there are potential concerns and complications associated with their widespread use in

the clinical environment such as osteonecrosis of the jaw. Recently, two monoclonal antibodies romosozumab and denosumab were introduced based on the discovery of sclerostin in restricting the differentiation of osteoblasts and the formation of osteoclast sustained by the receptor activator of nuclear factor kappa-B ligand (RANKL). In the United States, teriparatide and abaloparatide are the two other anabolic pharmaceutical agents approved to treat osteoporosis and they have been shown to reduce the incidence of non-vertebral and vertebral fractures significantly after they were administered to patients daily as subcutaneous injections.

Written by international experts from different specialties based in Australia, Italy, Malaysia, and the United States, it is envisaged that this book will provide readers with fundamental insights into the basic properties of the pharmaceutical agents used in the treatment of osteoporosis as well as their mechanisms of action and clinical outcomes. We also include topics covering the clinical application of osteoporosis treatments that would be of interest to a wide range of audiences involved in osteoporosis care including primary care physicians, endocrinologists, rheumatologists, orthopedic surgeons, and dentists.

Finally, we would like to express our deepest gratitude to all our contributing authors and the people at Springer Publishing, especially Dr. Ramesh Premnath, Ramamoorthy Rajangam, and Mano Priya Saravanan for their help and for making the book possible.

Sydney, Australia — Andy H. Choi
Hawaii, USA — Sian Yik Lim

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About the Editors

Dr. Andy H. Choi is an early career researcher who received his Ph.D. from the University of Technology Sydney (UTS) in Australia in 2004 on the use of computer modelling and simulation known as finite element analysis (FEA) to examine the biomechanical behavior of implants installed into a human mandible. After completing his Ph.D., he expanded his research focus from FEA to sol-gel synthesis of multifunctional calcium phosphate nano coatings and nano composite coatings for dental and biomedical applications.

In late 2010, Dr. Choi was successfully awarded the internationally competitive Endeavour Australia Cheung Kong Research Fellowship Award and undertook post-doctoral training at the Faculty of Dentistry of the University of Hong Kong focusing on the application of FEA in dentistry and the development of calcium phosphate nano-bioceramics.

He is currently serving as an associate editor for the Journal of the Australian Ceramic Society and as an editor for a number of dentistry-related journals. In addition, he is also serving as an editorial board member for several dentistry, nanotechnology, and orthopedics journals. To date, Dr. Choi has published over 50 publications including 5 books and 30 book chapters on calcium phosphate, nano-biomaterial coatings, sol-gel technology, marine structures, drug delivery, tissue engineering, and finite element analysis in nanomedicine and dentistry.

Dr. Sian Yik Lim is a rheumatologist at Pali Momi Bone and Joint Center, Hawaii Pacific Health. He currently runs a specialty osteoporosis clinic at Pali Momi Bone and Joint Center and has been involved in efforts to improve the quality of osteoporosis care in Hawaii. He is a clinical densitometrist certified by the International Society for Clinical Densitometry. After graduating from Osaka University School of Medicine, he subsequently trained in internal medicine and rheumatology in the United States. He completed his rheumatology fellowship at Massachusetts General Hospital and was a research fellow at Harvard Medical School. He has received the American Federation of Medical Research Resident Research Day Award and

Marshal J Schiff, MD Memorial Fellow Research Award for his research. He has published more than 30 papers and abstracts about gout, osteoporosis, and septic arthritis in respected journals such as JAMA, rheumatology, and current opinions in rheumatology.

Bisphosphonates: Clinical Applications and Perspectives in Osteoporosis Treatment

Sian Yik Lim and Marcy B. Bolster

Abstract Osteoporosis is a skeletal disorder characterized by decreased bone strength, leading to increased fracture risk. In this article, we discuss the use of bisphosphonates in the treatment of osteoporosis. We aim to give the reader a strong background of using bisphosphonates in osteoporosis treatment. We also discuss important topics pertinent to clinical care, including the potential side effects and adverse effects, as well as strategies to mitigate them. We also describe the long-term use of bisphosphonates with efficacy and safety in mind. We hope to provide clinicians with information that will be useful in daily practice when prescribing bisphosphonates for the treatment of osteoporosis.

Keywords Osteoporosis · Bisphosphonates · Skeletal disorder

1 Introduction

Osteoporosis is a skeletal disorder, characterized by reduced bone strength, leading to an increased fracture risk [1]. Fragility fractures related to osteoporosis are associated with significant morbidity, mortality, and health care costs. The management of osteoporosis focuses on reducing fracture risk. This article discusses bisphosphonates, one of the first medicines used to treat osteoporosis.

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While bisphosphonates were first synthesized in the 1800s, their use in medicine started in the 1960s. In the 1960s, William Neuman and Herbert Fleisch identified inorganic pyrophosphate in the urine and serum of study subjects. They postulated that inorganic pyrophosphate was potentially a natural water softener that prevented soft tissue calcification and potentially could be used to treat osteoporosis. However, pyrophosphate was only active when injected and not active orally because of the hydrolysis of pyrophosphate in the gastrointestinal tract.

Bisphosphonates, on the other hand, are stable even when given orally. This stability was a key reason for bisphosphonates being developed for medical uses. Bisphosphonates, like inorganic pyrophosphate, not only inhibited calcification in the human body but also had unique properties of inhibiting calcium phosphate dissolution [2]. This property was extrapolated for the possible treatment of bone disease, with studies evaluating their potential to inhibit bone resorption.

2 Chemical Structure of Bisphosphonates

2.1 Basic Chemical Structure of Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate, and the general structure is shown in Fig. 1 (left). Inorganic pyrophosphate (Fig. 1 (right)) is a naturally occurring compound in the body, released as a byproduct of synthetic reactions in the body [3]. Pyrophosphate inhibits calcification by binding to hydroxyapatite crystals in bone. However, because it is degraded rapidly by pyrophosphatases, it exhibits very little biological activity in vivo. Substitution of the oxygen atom in pyrophosphate by a carbon atom (Fig. 1a) produces a chemically stable bisphosphonate structure.

Two carbon phosphorus (C-P) bonds sharing a single carbon atom (P-C-P) are called germinal bisphosphonates resistant to enzymatic hydrolysis [3, 4]. Most bisphosphonates used in clinical practice have a hydroxyl group in the R1 position. The phosphate and hydroxyl groups are essential for the affinity of bisphosphonates

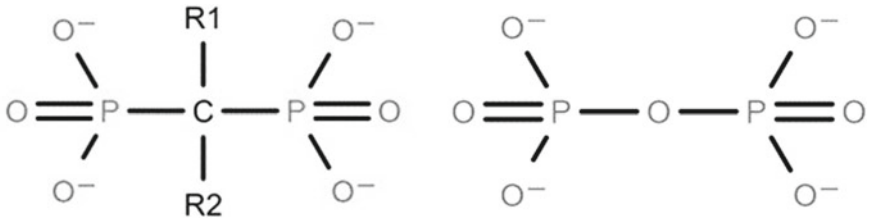

Fig. 1 The general chemical structure of bisphosphonate (left), and inorganic pyrophosphate (right)