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Review Article

Osteoporosis and its Management: A Timely Update

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Abstract

The National Institutes of Health defines osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. However, currently there is no definition that is agreeable to both medical and scientific communities and its etiology is poorly understood. It is within this framework that the pharmaceutical industry is trying to develop new treatments for the so-called silent epidemic. This review article describes the osteoporosis as a disease and look forward for the update in its management. The current review has been done using PubMed and Medline search with keywords.

Introduction

Osteoporosis is a disease that is understood by those working within the subspecialty, but currently there is no definition that is agreeable to both medical and scientific communities and its etiology is poorly understood. It is within this framework that the pharmaceutical industry is trying to develop new treatments for the so-called silent epidemic. In layman's terms, the disease of osteoporosis is defined as brittle bones occurring in the elderly that could lead to fractures.

The classical definition was "a bony fracture caused by minimal trauma owing to a loss in bone mineral." A published consensus definition states that osteoporosis is "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures". The National Institutes of Health (NIH) Consensus Conference Statement on Osteoporosis Prevention, Diagnosis, and Therapy states that "osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture". The World Health Organization (WHO) operationally defines osteoporosis as "bone density 2.5 standard deviations (SDs) below the mean for young white adult women at lumbar spine, femoral neck, or forearm".

It is now recommended that the diagnostic use of this definition is restricted to bone density of the femur. Although it is not clear how to apply this in men and children, it is recommended that the same diagnostic thresholds can be used in men. The NIH statement recognizes that bone strength reflects the integration of two main features: bone density and bone quality. Currently, there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70% of bone strength. Thus, osteoporosis has become a disease that is characterized by measurement of BMD.

The endpoint of many clinical trials is BMD, either used as a primary endpoint in its own right or used as a surrogate marker for fracture risk. Regulatory authorities tend to consider osteoporosis in terms of fracture when it comes to licensing new treatments for the management of the disease and increasingly, BMD for the prevention of osteoporosis. It is, therefore, imperative that the researcher understands which definition of the disease they are using and what the endpoint or hypothesis they are trying to evaluate is before they embark on a research

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program. Second, because osteoporosis is a disease that is diagnosed using a measurement of BMD and is monitored over many years using such measurements, there are a range of technical issues to ensure the quality and consistency of BMD measurements that must be considered. Several of these relate to the choice of equipment, standardization, and quality control before a trial begins, in addition to technical issues that must be considered throughout the life of the study. Third, osteoporosis trials are often long-term trials carried out in normal, asymptomatic women, in whom proven drugs for the treatment and prevention of osteoporosis are already licensed. This is particularly true of clinical trials in women who are close to the menopause. This presents ethical issues because the latest version of the Declaration of Helsinki (Finland), produced in Edinburgh (UK) in 2000, specifically states that placebo control in the presence of a proven treatment is unethical. This conflicts with the requirements of the US Food and Drug Administration (FDA), which still requires placebo control for licensing purposes. These women are also unlikely to gain any direct benefit from a short-term trial, which raises other ethical issues. Postmenopausal women (aged 55 to 65 years) are unlikely to have any long-term reduction in fracture risk if the fracture does not occur until they are aged 80 years. Any protective effect of treatment will have worn off. What happens at the end of the study? Will treatment still be available to subjects if a proven treatment effect is demonstrated? In summary, the definition of osteoporosis is not universally agreed, it is a disease defined by a measurement of BMD and often clinical trials are carried out in normal, asymptomatic women. For researchers entering into this therapeutic area, it seems to be initially confusing and technically challenging. On this basis, osteoporosis clinical trials deserve a work that provides an introduction to the novice and clearly explains the design and implementation of these trials.

Fractures

Fracture is the most significant consequence of osteoporosis. Although osteoporosis can affect any bone in the body, the most typical sites of fractures related to osteoporosis are the hip, spine, and wrist (NOF, 2006). Of the 1.5 million fractures that occur in the United States each year, 20% occur at the hip, 50% in the spine, and 30% at the wrist and other sites. The annual worldwide incidence of fracture was estimated to be 1.29 million in l990, and is projected to grow to 2.6 million by 2025 and to 4.5 million by 2050 (WHO, 2003). The highest fracture rates are reported from northern Europe, the northern part of the United States, and among Southeast Asian populations, with the lowest rate from African countries. The risk of hip fracture among Norwegians is four time that of southern Europeans and double that of Americans. It is of note that the differences in incidence of hip fractures between countries are greater than the differences between genders. Fracture site is also age related. For individuals in their 50s, wrist fractures are most common. Individuals in their 60s are more likely to sustain fractures of the vertebrae of the spine, and by the time an individual reaches the 70s, the hip becomes the most common site of osteoporotic fracture. The rates of all three types of fracture increase with age, but the increased risk with aging is most pronounced for hip fractures.

The monetary costs associated with osteoporotic fractures are sobering. In l995, osteoporosis resulted in 423,000 hospital admissions, 800,000 emergency room visits, 180,000 nursing home admissions, and 2.5 million physician's office visits. In the United States alone, the annual direct cost for medical care associated with osteoporotic fractures was osteoporosis estimated to be between $12.2 and $17.9 billion in 2002, with each hip fracture costing $40,000 in medical costs. Spinal fractures are considerably less problematic in terms of cost, with only 10% requiring hospitalization and fewer than 2% being admitted to a nursing home. However, they account for 66,000 physician's office visits and at least 45,000 hospital admissions each year. Since most of these fractures occur among older adults who are no longer employed, these figures are not heavily weighted by loss of wages. Rather, the costs are associated with direct care services: inpatient care (62%), nursing home care (28%), and outpatient service (10%). Hip fractures account for about 63% of these costs, while fractures at other sites consume the remaining 37%. Given that 75% of all hip, spine, and distal forearm fractures occur in persons 65 years and older, a large portion of the direct costs is borne by society, in the form of social reimbursement programs. Even the least susceptible group to fracture, non-White men, required $174 million in osteoporosis care in 1995. The significant contribution of non-hip fractures in men and non-white groups to health care expenditures dispels any lingering misconceptions that the impact of osteoporosis is limited to hip fractures among older white women.

Global graying has become a commonplace reality—the population is living longer, and the proportion of old people within the population is growing. The fastest-growing segment of the population is the oldest-old (i.e., those age 85 years or more). Consider the ramifications of these demographic trends on the incidence of osteoporosis and fracture (both highly associated with increasing age). Global demographic changes are expected to dramatically increase the prevalence of osteoporosis. By 2050, it is estimated, the number of individuals age 65 and older will be nearly 1.55 billion worldwide. The increase among this population could result in an almost 4-fold increase in the number of hip fractures worldwide. That projection equates to a growth from 1.66 million

fractures in 1990 to 6.26 million fractures in 2050. The most significant increase in hip fracture rates is expected to occur in third world countries, particularly in Asia. Currently, Asia accounts for approximately 30% of global hip fractures. By 2050, it is expected to account for more than 50% of all hip fractures. It is imperative that due consideration be given to the collective impact of these fractures on the individual, the family, the community, and society. Osteoporotic fractures represent a phenomenal concern that demands our utmost attention if we are to avert the predicted rapidly increasing trend. Osteoporosis presents a major public health concern. Arresting this preventable disorder must be a major focus of global preventive efforts in this century.

Bone

Bones can be conveniently divided into flat bones such asthe scapula, skull, and pelvis, and tubular bones which include the limb bones and vertebral bodies. The dense outer surface or cortex is composed of compact bone and the centre or medulla is braced by narrow plates or trabeculae, a construction which gives maximum strength for minimum weight. In the interstices of the medulla lies the bone marrow, where bone cells are in close contact with haemopoietic cells.

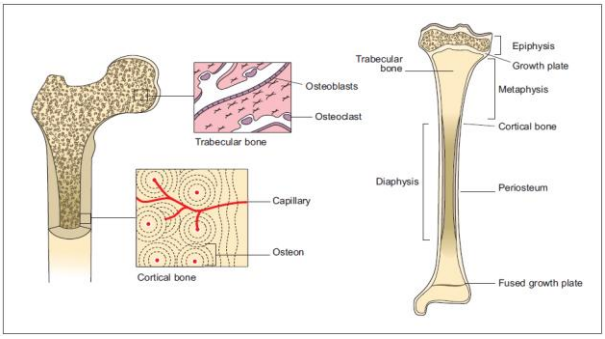

Figure 1. Structure of bone.

Cortical bone: Cortical (compact) bone constitutes 75–80% of the skeletal mass. It forms the outer surface of all bone but the majority is found in the shafts of tubular bone. Compact bone is composed of lamellae which are concentrically arranged around a small central canal to form a Haversian system or osteon.
Trabecular bone: Trabecular bone is a rigid meshwork of mineralized bone which forms the greater part of each vertebral body and the epiphyses of the long bones, and is present at other sites such as the iliac crest. It contributes 20% of the total skeletal mass, but 65–70% of the total bone surface.Complete struts are called trabeculae, but incomplete spicules are also seen.
Bone composition: The fundamental constituents of bone are the cells and the extracellular matrix.

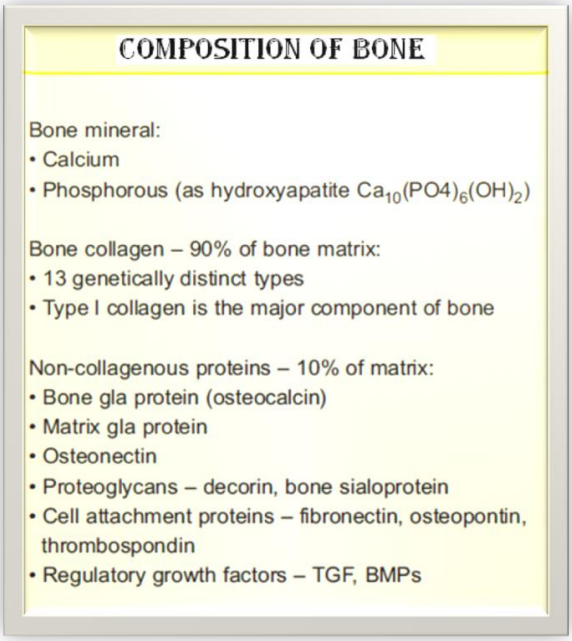

Figure 2. Composition of bone.

Bone cells: *Osteoblasts:* Osteoblasts are responsible for producing bone matrix constituents, chiefly collagen and noncollagenous matrix proteins that form osteoid. They control mineralization of bone. They originate from bone marrow stromal or connective tissue mesenchymal stem cells which proliferate and differentiate into preosteoblasts and then mature osteoblasts, after being subject to different stimulations of local growth factors and transcription factors. Osteoblasts are found in clusters of up to about 400 cells at a bone-forming site. Surface osteoblast or lining cells line inactive trabecular surfaces. Activated osteoblasts line the layer of bone matrix they are making, the osteoid surface, and prior to calcification. Their cellular structure reflects their high synthetic and secretory activity with a well-developed rough endoplasmic reticulum and large golgi complex and a number of more or less bone-specific proteins, collagen type I in particular, are secreted. The plasma membrane of the osteoblast is rich in alkaline phosphatase (ALP) and the ALP activity increases early in the mineralization phase. Osteoclasts have cell surface receptors for hormones including parathyroid hormone, vitamin D, and oestrogen, but also cytokine receptors. There is a close linkage between osteoblast and osteoclast activation, and cells of osteoblast lineage secrete cytokines that participate in osteoclastogensesis. Osteoblasts express cytokines on their surface including RANK ligand (RANKL) which, through interaction with RANK, promotes bone resorption. Osteoprotegerin is also secreted by osteoblasts, which is a decoy RANK receptor that can inhibit osteoclast formation. After forming bone, some osteoblasts are embedded in the mineralized matrix and become osteocytes, some remain on the surface and become

bone-lining cells, whereas others will undergo apoptosis (programmed cell death).

Osteocytes: Osteocytes are embedded deep within bone in small lacunae, having originated as osteoblasts and becoming trapped in the matrix they produced. They have numerous long cell processes which are in contact with other osteocytes and lining cells on the bone surface. They are surrounded by the periosteocytic space which is filled with extracellular fluid. Osteocytes have a role in maintaining extracellular calcium concentration. They may also act as mechanoreceptors and in the local activation of bone remodelling.

Osteoclasts: Osteoclasts are responsible for bone resorption. They are giant, multinucleated cells usually found in contact with calcified bone surface within lacunae that result from their resorptive activity. An activated resorption site may contain from one to five osteoclasts. Osteoclasts have a different origin from osteoblasts. They are derived from hematopoetic stem cells and are related to macrophages. Mature osteoclasts are formed by the fusion of osteoclast precursors. Osteoclast differentiation is promoted by the interaction of RANK expressed on osteoclasts and RANKL. They have abundant Golgi complexes, mitochondria, and transport vesicles containing lysosomal enzymes. Osteoclasts form sealed bone-resorbing compartments next to the bone surface, with a ruffled border formed by deep folding of the plasma membrane facing the bone matrix. They undergo apoptosis after they have finished resorbing bone.

Factors that influence bone strength: Bone is an organ that gives form to the body, supporting its weight, protecting vital organs, and facilitating locomotion by providing attachments for muscles to act as levers. It also acts as a reserve for ions, especially calcium and phosphate, the homeostasis of which is essential to life. It is composed of cells and extracellular matrix, like other connective tissues, but the matrix has the unique ability to be calcified. The strength of a bone and its ability to perform these physical functions depend on its structure and the intrinsic properties of the materials of which it is composed. The amount of bone (bone size, mass, and density), its spatial arrangement (shape, geometry, and microarchitecture), its composition (intrinsic properties of bone materials), and its turnover (rate and balance of formation and resorption) are all such determinants of its ability to perform mechanical functions and to resist fracture.

Bone matrix and mineral: The extracellular matix is a 'composite' in materials science terms, a matrix comprised of collagen and ground substance that is mineralized. Crystals of hydroxyapatite are precipitated on the collagen fibres. The mineral phase gives compressive strength and rigidity, but it is the fibrous organic matrix that gives bone its resistance to tractional and torsional forces. The mineral phase accounts for up to 70% of adult bone. Collagen forms 90% of bone matrix, of which type 1 is pyridinium rings so that pyridinium cross-links are formed, connecting three different collagen molecules. These cross links are described as pyridinoline or deoxypyridinoline cross-links, depending on the combination of hydroxylysine and lysine side residues. The cross-linking is specific for each of the N- and C-terminal telopeptide regions, and is also relatively bone-specific5. The orientation of the collagen fibres alternates from layer to layer in adult bone, which gives the typical lamellar structure seen by polarizing light or electron microscopy. the major component. Noncollagenous proteins form the ground substance, primarily glycoproteins and proteoglycans, but there are other matrix proteins present in small amounts that have important although not fully characterized roles. Most but not all of these noncollagenous proteins are synthesized by bone cells. Type I collagen is formed in bone from the combination of two collagen polypeptides containing hydroxylated proline and lysine residues. It is secreted as pro-collagen from the osteoblast, when the amino-terminal and carboxy-terminal regions are cleaved. Type I collagen is helical; the non helical domains at the amino- and carboxytermini are known as the N-telopeptide and C-telopeptide regions. The structure of type I collagen is stabilized by side chains of hydroxylysine residues which condense to form.

Bone morphogenetic protein: Bone is a complex tissue composed of several cell types which are continuously undergoing a process of renewal and repair termed "bone remodeling". The two major cell types responsible for bone remodeling are osteoclasts, which resorb bone, and osteoblasts, which form new bone. Osteoporosis is a reduction in skeletal mass due to an imbalance between bone resorption and bone formation. Bone morphogenetic protein (BMP) plays important roles in osteoblastic differentiation and bone formation. Therefore, components involved in BMP activation are good targets for the development of anti-osteoporotic drugs. Bone morphogenetic proteins (BMPs), with more than 20 members, belong to the TGF-β superfamily and were originally identified by their unique ability to induce ectopic cartilage and bone formation *in vivo*. It has been shown that BMP-2 and BMP-4 are synthesized by osteoblasts. BMPs play important roles in bone formation and bone cell differentiation BMPs bind to specific heteromeric complexes of two related serine/threonine kinase receptors, type I and type II receptors. Three BMP type I receptors (BMPRIA/ALK-3, BMPRIB/ALK-6 and BMPR2) and three BMP type II receptors (ACVR1, ACVR2, ACVR2B) have been characterized. Signaling by BMP proteins is mediated through (heterodimeriziation of types I and II serine/threonine kinase receptors).

BMPs stimulation results in the activation of transcription factors activated by TGF-β (SMAD) proteins, which then accumulates in nucleus and control transcription of a large number of target genes. SMAD1, SMAD5, and SMAD8 are recognized by

BMP type I receptor. BMPs also activate extracellular signal-regulated protein (ERK) 1/2, and c-Jun NH2 terminal kinases mitogen-activated proteins kinases (MAPKs) via SMADs-independent pathway. The function of BMPs is highly diverse, acting on many different cell types, such as epithelial, mesenchymal, and neuronal cells, thereby regulating proliferation, differentiation, chemotaxis, and apoptosis of these cells. BMPs exert a central function in embryonic development, from the very early establishment of the dorsal/ventral body axis to the later formation of organs, e.g., kidney, eye, limb, amnion, heart, and testis. Because of their omnipresent character, failure as well as deregulation of BMP signalling leads to severe diseases, e.g., skeletal abnormalities or metabolic disorders [6]. A hallmark of the BMP super family is its highly promiscuous ligand-receptor interaction. BMP-2 binds to the two type I receptors, BMPR-IA and BMPR-IB, with almost identical affinity. In addition, three different type II receptors, BMPR-II and activin type II receptors ActR-II and ActRIIB, can be recruited into the complex alike, leading to similar SMAD activation. During the past years, several structures of BMPs bound to the extracellular domains (ECD) of type I and type II receptors have been published, yielding a first glimpse into how binding affinity is generated and how promiscuous binding to different type I and type II receptors might be achieved. To date, three crystal structures of BMPR-IAECD bound to BMP-2 have been determined, showing that irrespective of crystallization conditions the binding and structure of BMPR-IAECD are basically identical in all three cases.

Most members of the TGF-b super family are unable to bind to their type I receptors in the absence of the corresponding type II receptors[14].In contrast, BMP binds to its type I and type II receptors independently, even though trimeric complex formation between these three molecules is necessary for its signaling. In this sense, BMP is unique among the TGF-b super family, and provides an opportunity to study direct interactions between the ligand and the type I receptor. The interface of BMP-2 and BMPRIA is distinct from other growth factor receptor interfaces. The binding epitope of BMP-2 is highly hydrophobic, with almost 60% of contact surface area of 1,150 Å provided by hydrophobic residues. As compared to binding epitopes of other growth factors as human growth hormone, interleuckin-4, erythropoteins or interleuckin-6 the hydrophobic contact area of BMP-2 is quite large also similar findings seen in BMP-7 with activin receptor II, TGF-*ß3* and activin with their respective receptors. In contrast the binding epitope of BMPRIA is less hydrophobic (30%) owing to a stretch of polar and charged residues running across binding interface. There are ten intra molecular hydrogen bonds in single BMP-2/ BMPRIA [20] complex. The residues engaged in binding are Phe49-Asn59 and short alpha helix and sequence like (As84-Arg97). The two hydrogen bonds BMP-2 Asp53 Cys77 and BMP-2 Ser69 and Gln94 are formed between side chain and man chain atoms.

While in the binary and ternary ligand-receptor complexes of BMP-2 the α-helices of BMPR-IA comprising residues Gly83-Lys88 are identical with respect to backbone and side chain conformations, this helix is completely absent in the structure of the free receptor. The comparison of BMPRIA in its free and ligand-bound forms shows that the five central *ß*-strands forming a three-finger toxin-like fold are rigid and are structurally well conserved. In contrast, two loops connecting strands *ß1* and *ß2* as well as strands*ß4* and *ß5* undergo significant conformational rearrangements upon ligand binding. The *ß4- ß5* loop of BMPR-IA switches between two conformations, random coil in the unbound state and a short 1.6-turn helix in the bound state, depending on whether BMPR-IA is bound to its ligand or BMPR-IA is free in solution. Interestingly, the main binding determinants of BMPR-IA, Phe85 and Gln86, for the BMP-2-BMPR-IA interaction are located in this highly flexible region. Interactions between Phe85 and Gln86 of BMPRIA and residues of BMP-2 can only be established if the helix R1 is present, implying that a substantial part of the binding free energy can be generated only with a large induced fit of the *ß4-ß5* loop. Comparison of BMP-2 in its free and bound state reveals that the type I receptor epitope of BMP-2 (wrist epitope) also undergoes an induced fit upon type I receptor binding. Compactin, simvastatin, coumarin derivatives such as imperactorin, bergapten are reported as inducers of BMP in osteoblast differentiation and p38 ERK dependent pathway in osteoblast differentiation by stimulating alkaline phosphatase (ALP) activity and synthesis of proteoglycan, collagen, fibronectin and osteocalcin.

Activation of BMP-receptors: BMP signaling is fine tuned at multiple levels, beginning with ligand binding to its receptors, activation of the receptors, and downstream when signals enter the nucleus.BMP2 signals *via* two trans membrane serine/threonine kinase receptors BMPRI and BMPRII. Studies that the canonical Smad pathway is initiated at preformed receptor complexes (PFC, composed of BMPRI and BMPRII), which exist in an inactive state in the plasma membrane and get activated upon BMP2 binding. BMP2 binding to monomeric BMPRI causes dimerization of this receptor which subsequently leads to the recruitment of BMPRII into the signaling complex; these receptor complexes are called BMP2-induced signaling complexes (BISC). The signaling cascade which is initiated at BISCs involves p38-MAPK as opposed to Smads resulting in the induction of Alkaline phosphatase (ALP).

BMP receptor family plays some important roles in human body starting from embryogenesis to cancer regulation. The proteins are also important in embryo development and tissue regeneration. Some of the BMPs are also known to be important players in cancer**.** For example, BMP-2, BMP-6 and BMP-7 have

been shown to be aberrantly expressed in human cancers and that raised levels of the proteins either in the circulation or in tumors are associated with progression and spread of cancer. Loss-of-function mutations in bone morphogenetic protein receptor II (BMP-RII) are linked to pulmonary arterial hypertension (PAH). Knockout of BMP-2 and BMP- 4 results in defects in mesoderm formation. Mutations in BMP 5 in mice are responsible for the short ear phenotype. BMP-7 null mice exhibit defects in eye, kidney and skeleton. BMP-4 stimulates chondrogenesis in limb bud mesenchymal cells and maintains articular cartilage phenotype. BMPs are thus critical for bone and cartilage morphogenesis and beyond. BMPs should perhaps be called body morphogenetic proteins, which would take into account the wide-ranging actions of BMPs and obviate the need for tinkering with terminology.

Currently Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been commercially available in the United States since July 2002. It was initially approved for use in anterior lumbar inter body fusions with an inter body cage. It has been further approved for two additional clinical indications: fresh tibial fractures and certain oral maxillofacial procedures. But this technique also had some limitations as compression resistance inhibitions of carrier (Absorbable collagen sponge INFUSE® Bone Graft) molecules for rhBMP-2. In kidney development, transient inhibition of BMP-4 activity by Gremlin (a BMP antagonist) is essential in ureteric bud outgrowth, while BMP-7 functions as a survival factor for metanephric mesenchyme. Animal studies demonstrating that BMP-7, BMP-2 and GDF-5 (also called CDMP-2 or MP-52) have various abilities to repair cartilage in models of degenerated articular cartilage, including focal osteochondral and chondral defects and osteoarthritis, as well as models of degenerated intervertebral disc cartilage. Together, findings indicate a significant promise for BMPs and particularly BMP-7 as therapeutics for cartilage repair and regeneration. Due to their multiple regenerative activities, BMPs have been systemically tested in preclinical models for the following indications: bone formation in a model of osteoporosis, kidney regeneration in models of acute and chronic renal failure, liver regeneration, ischemic coronary infarction and stroke, and in a nude mouse model of different human cancers. These studies suggested that following their systemic use, BMPs support organ regeneration recapitulating the embryonic development and therefore might serve as novel molecules in regenerative medicine.

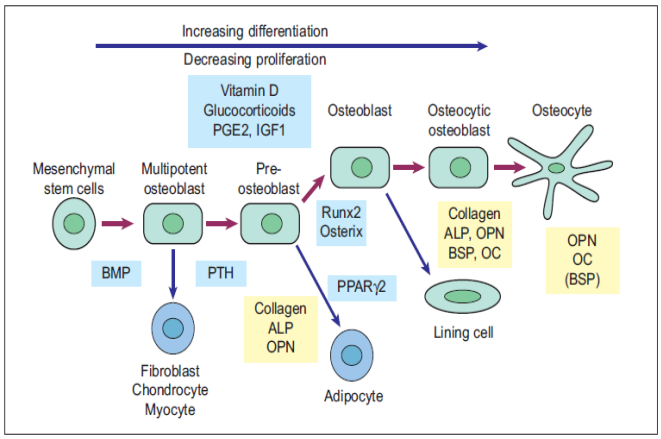

Figure 3. Osteoblast formation

Bone turnover and remodeling: Bone may seem inert but is a dynamic tissue and continually turns over throughout life. Maintenance of bone integrity relies on a closely controlled balance between osteoblastic bone formation and osteoclastic bone resorption. The initial phase of growth of the skeleton during childhood and adolescence is associated with increasing bone density and rigidity. This is followed by a phase through adulthood when there is a close coupling between formation and resorption and the bone mass is stable, but turnover allows continual renewal and repair of the skeleton. In later life there is an imbalance with a net loss of bone mass from both the trabecular and cortical compartments, which may lead to osteoporosis.

MARKERS OF BONE TURNOVER

Bone formation

Serum

- Osteocalcin
- Bone-specific alkaline phosphatase
- Type I collagen C- and N-propeptide (PICP and PINP)

Bone resorption

Serum

- Free pyridinoline and deoxypyridinoline
- Pyridinoline cross-linking telopeptides (C- and N-telopeptides, CTx, NTx, ICTP)
- Tartrate-resistant acid phosphatase 5b
- Bone sialoprotein

Urine

- Pyridinoline crossliinks (pyridinoline and deoxypyridinoline)
- Pyridinoline cross-linking telopeptides (C- and N-telopeptides, CTx, NTx, ICTP)
- Osteocalcin fragments
- Hydroxyproline
- Calcium

Figure 4. Markers of bone turnover.

Markers of bone turnover: During bone turnover, surplus products synthesized by the osteoblasts during bone formation or fragments released during

bone resorption are found in blood and urine. The levels of these can be used as markers of bone formation, resorption, and rate of turnover. Osteoblast-associated proteins are differentially expressed during bone formation and could ideally provide information on the formation process. However, when systemically assessed the sensitivity is insufficient. The bone specific iso-enzyme of ALP increases early during mineralization. Osteocalcin, the most abundant noncollagenous protein, increases when mineralization is in progression and in differentiated osteoblast when also bone sialo protein is expressed. Breakdown of bone tissue liberates collagen fragments and the terminal ends

Current Therapies for Osteoporosis

Osteoporosis is a relatively new clinical area that is perhaps best viewed as a preventable and treatable risk factor for fragility fracture. Treatments with robust evidence from randomized, controlled trials (RCTs) have only become available in the last 20 years, and the most widely prescribed legacy treatment, in the form of hormone-replacement therapy (HRT), is rarely used nowadays. This chapter does not dwell on the public health issues associated with the prevention of osteoporosis and the attainment and maintenance of optimum bone health through exercise, diet, and avoidance of smoking and excess alcohol. These are important issues, but they are beyond the scope of this pharmacological view. The interaction between osteoporosis and falls is, however, briefly considered because both are risk factors for fracture.

Osteoporosis is becoming a major healthcare problem because of its association with fragility fractures. A number of independent and semi independent skeletal and non skeletal risk factors enhance the ability of bone mineral density (BMD) to predict future fracture risk. Age is the greatest predictor of an individual's risk of fracture and we are set to see a rapid rise in incidence of fracture as the population of older people increases, with greater longevity. The personal and health economic burdens are huge. The clinical consequences of painful fracture cause 189 increased mortality, debility, dependence on social care, and a reduced quality of life. It is conservatively estimated that the health and social care consequences of osteoporotic fractures are as much as US$ 3.3 billion annually. This could be a significant underestimate because more recent research has suggested the in-patient costs of hip fracture might be more than double that used to arrive at the above figure and that hip fractures that involve nursing home care might also be far more costly than earlier estimates suggested. In addition, fractures in subjects over 60 years old account for more than 2 million bed days each year in England alone. Despite this, there is consistent evidence that, even the highest risk subjects, such as those with prior fragility fracture, are under identified and undertreated in both primary and secondary care. The diagnostic threshold has been based on measures of bone mass and the World Health Organization (WHO) defined osteoporosis as "a bone mass at the hip that is more than 2.5 standard deviations (SD) below the mean of a young woman at peak bone mass." This age-independent measure of BMD came to be known as "the T-score." It is important to remember that this diagnostic cut-off point was defined for epidemiological reasons and is not, in itself, an intervention threshold. Indeed, over a reasonable timescale, the majority of fractures will occur in subjects who did not have osteoporosis at baseline. Nevertheless, treatments will be discussed that have been shown to both improve BMD and reduce future fracture risk in subjects with osteoporosis both with and without a history of prior fragility fracture. Only a proportion of the fracture risk reduction is explained by improvement in BMD and the pharmacological actions of these therapies are almost certainly more complex than just their ability to increase bone mass. A number of clinical risk factors seem to act as proxies of other characteristics of bone quality and help clinicians target therapies cost-effectively at those with the highest risk.

There are other considerations, such as bone geometry and biochemical markers of increased bone turnover, that are also associated with a higher fracture risk but they are not as yet sufficiently quantified to be useful in case finding. Probably the best way to make rational decisions about who to treat is look at their absolute fracture risk by site over a 5 to 10 year period of time and this is a current objective of the WHO. A fracture-risk assessment tool similar to those used to predict the risk of cardiovascular disease is under development.

Characteristics of Available Treatments: Therapies for osteoporosis are licensed for either prevention or treatment, or both this distinction is somewhat artificial and whether a treatment is used in either 190 Jonathan R. Bayly way will tend to depend more on the balance between risks and benefits and whether the treatment is acceptable to the subject and cost-effective. Osteoporosis itself is asymptomatic and its clinical significance is that it is an important modifiable risk factor for low-trauma fracture. When selecting a therapy, it is more relevant that the treatment has anti-fracture efficacy and to determine whether this efficacy is for both vertebral and non vertebral fractures, particularly including hip fracture because this is the most costly fracture to the subject and society. Figure 3.1 and Figure 3.2 illustrate the different effects of four different osteoporosis treatments on vertebral and non vertebral fractures in a meta analysis of published trials.

Other desirable characteristics of a pharmacological intervention for osteoporosis are safety and tolerability. Ideally, a preparation should be easy to take because this will improve the chances of both compliance and persistence with treatment. Cost-

effectiveness is increasingly determining which preparations healthcare organizations will permit clinicians to prescribe and in England; the National Institute for Health and Clinical Effectiveness (NICE) and the activities of prescribing advisers and formulary committees are very influential in this process. It must be remembered that the majority of the RCTs that have been published are in Caucasian postmenopausal women. There are substantial variations in the prevalence of osteoporosis and osteoporotic fractures in different countries, even in this group of subjects. Although probably equally effective in men, the evidence base is limited. We have little knowledge of the efficacy of treatments in racial groups other than Caucasians, in which the absolute fracture risk could be much lower and, therefore, cost-effectiveness more difficult to demonstrate. Bone is a dynamic tissue that is constantly remodelling through the activity of osteoclasts and osteoblasts, whose function is modulated by skeletal and extra skeletal signaling that is beyond the scope of this chapter. Treatments for osteoporosis aimed at reducing fractures can broadly be divided into three groups: those that reduce resorption by inhibiting osteoclastic activity, those that have anabolic functions that stimulate osteoblastic activity to lay down more bone, and one preparation that seems to have a dual action. Finally, vitamin D and calcium are both integral to bone health and their role in the management of osteoporosis will also be discussed. Virtually all the RCTs described below that have fracture as an outcome attempted to ensure subjects were replete in both calcium and vitamin D.

Hormone Eeplacement Therapy (HRT): HRT has historically been the mainstay of treatment for those with osteoporosis or who are at risk of osteoporosis. There was, for some time, good evidence for the prevention of postmenopausal bone loss and some limited evidence from observational studies that suggested HRT reduced fractures. The major use of HRT was, however, in the perimenopausal and immediately postmenopausal woman and the criticism was that treating younger women in their late 50s and early 60s was not likely to have a great impact on the incidence of vertebral and hip fractures in their 70s and 80s because the benefits of HRT seemed to be rapidly lost on discontinuation. Ironically, it was the same RCT, the Women's Health Initiative (WHI) study, which finally produced convincing evidence for efficacy in reducing fractures while it demonstrated an unacceptable increased risk in thromboembolic side effects, stroke, coronary heart disease, and breast cancer. Although the study has had many critics and the absolute risk of adverse events was quite low, particularly in younger women, it has effectively signalled the end of HRT as a widely used preparation for osteoporosis. It still has a role in the treatment of women needing bone protection after suffering a menopause well before the modal age, but other 192 Jonathan R. Bayly uses require careful risk evaluation in partnership with the subject, especially if a combined preparation is to be used if the incidence of adverse events seems higher than in subjects treated with unopposed oestrogen.

Selective Oestrogen Receptor Modulators (SERMs): *Raloxifene*: Evista Eli Lilly and Company, Indianapolis, USA, at a dose of 60 mg/day, is the only current product of this class available for osteoporosis. The definitive study was the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.[18] Raloxifene is licensed for the prophylaxis and treatment of osteoporosis in postmenopausal women. Drugs of this class have both agonist and antagonistic actions on oestrogen receptors. Raloxifene has positive oestrogenic effects on bone. It prevents bone loss but does not stimulate breast or uterine tissues.[19] It has beneficial effects on low-density lipoproteins, raising the possibility of cardiovascular benefits.[20] The MORE study compared the effects of raloxifene, 60 mg/day and 120 mg/day, with placebo over a period of 4 years in more than 7000 postmenopausal women, with a mean age of 67 years (range, 31–80 years), who had either osteoporosis (a BMDT-score of_2.5 at the hip or spine) or a morphometric vertebral fracture. Other bone remodelling agents were allowed in the fourth year of treatment.

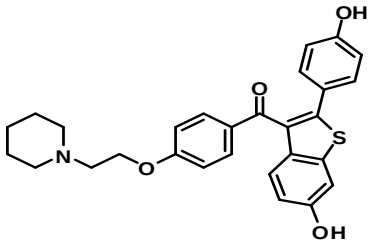

Figure 5. Structure of *raloxifene.*

BMD was significantly increased and markers of bone turnover were appropriately suppressed in the actively treated arm of the study. More importantly, there was a reduction in vertebral fracture compared with placebo. At 3 years, 6.6% of subjects treated with the licensed dose of raloxifene (60 mg/day) had sustained at least one new vertebral fracture compared with 10.1% of women receiving placebo. The relative risk (RR) was 0.7; the 95% confidence interval (CI) was 0.5–0.8. The greatest absolute risk reduction was, of course, seen in those with the highest absolute risk that is those with a prior vertebral fracture (Figure 33.2). No evidence was found that raloxifene reduced the risk of non vertebral fracture.

Women receiving raloxifene had an increased risk of venous thromboembolus compared with those receiving placebo (RR, 3.1; 95% CI, 1.5–6.2). Raloxifene did not cause vaginal bleeding or breast pain but there was an increased risk of hot flushes, leg cramps, and peripheral oedema. Breast cancer was significantly reduced in the MORE study (RR, 0.3; 95% CI, 0.2–0.6) and further analysis has confirmed a 90% reduction in oestrogen receptor positive breast cancer only. Data at 4 years found a 72% reduction in invasive breast cancer. The relative efficacy of

raloxifene compared with another SERM, tamoxifen, is currently being evaluated in the Study of Tamoxifen and Raloxifene (STAR) trial. Although there was no primary preventative effect in the MORE study at 4 years, there was evidence of a 40% reduction in cardiovascular events in a subset of just over 1000 women with known ischaemic heart disease.

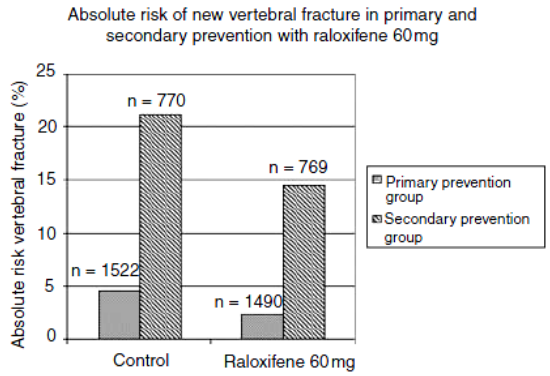

Figure 6. The differential effect of raloxifene in primary and secondary prevention of new vertebral fracture.

Bisphosphonates: Bisphosphonates are stable analogues of inorganic pyrophosphates, which have made a substantial contribution to the disease area and have come to dominate the market. They act as antiresorptives and all have evidence of effectiveness, that is they reduce markers of bone turnover, increase BMD, and reduce fractures, although not all bisphosphonates have evidence of efficacy both vertebral and non vertebral fractures. One characteristic of these preparations as a consequence of their mode of action and the cycle of the bone remodelling unit, is that they do not need to be taken daily. Indeed, the once weekly versions are now the most commonly prescribed formulation, but a monthly oral preparation is also available and a quarterly parenteral bisphosphonate for the treatment of osteoporosis is shortly to be released at the time of writing. Parenteral preparations of bisphosphonates, with infrequent dosing schedules, have been available for some time for the management of oncology. Because of the tendency of the oral preparations to cause upper gastrooesophageal symptoms and the almost complete failure of absorption if taken with food, rather complex administration instructions must be complied with. Medication, with the exception of etidronate, which can be swallowed in the middle of a 4-hour fast, should be taken first thing in the morning on an empty stomach with a full glass of tap water and in an upright position that is maintained for at least 30 minutes before food is consumed. Bisphosphonates are contraindicated in subjects with severe renal impairment whose glomerular filtration rate is 35 ml/min.

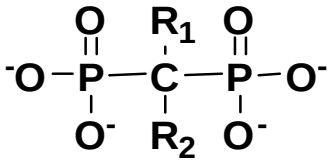

Figure 7. Bisphosphonates

Etidronate: Disodium etidronate (Didronel PMO, Procter & Gample Pharmaceuticals, Cincinnati, OH, USA) is licensed in the UK for prevention and treatment of osteoporosis in both men and postmenopausal women and treatment of glucocorticoid- induced osteoporosis (GCIOP). The drug is taken as a 14-day pulse of oral etidronate (400 mg), followed by 76 days of calcium supplementation. The original studies were rather limited and could be criticized for a number of reasons. Bayly Etidronate never gained a license in the USA as a result. There has never been any convincing evidence from RCTs for its effectiveness in hip fractures, which was only reported in an observational study and vertebral fracture efficacy was only seen in those with the most severe baseline disease. The drug is now used increasingly rarely and in 2005 only 4.2 % of osteoporosis-related prescriptions were for etidronate preparations.

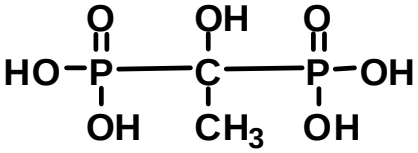

Figure 8. Structure of etidronate.

Alendronate: Alendronate (Fosamax, Merck & Co. Inc., Whitehouse Station, NJ, USA) is licensed for the treatment of osteoporosis in postmenopausal women and men and GCIOP. The drug is available at dosages of 5 mg/day, 10 mg/day, and 70 mg/week. The 10 mg/day and 70 mg/week doses are those for which trial evidence supports the best efficacy. The drug has recently become available generically, but at the time of writing, there is no generic daily dose available.

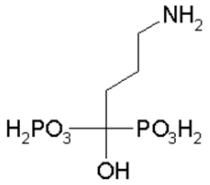

Figure 9. Structure of alendronate.

Alendronate is the most commonly prescribed bisphosphonate and has recently become available in combination with 400 IU of colecalciferol (vitamin D3) as Fosavance® , (Merck & Co. Inc., Whitehouse Station, NJ, USA). Alendronate is the most extensively studied bisphosphonate and has been shown to increase BMD and reduce the risk of vertebral, hip,

and other nonvertebral fractures in subjects with prior vertebral fracture and those with low BMD0.31–0.82).

Risedronate: Another bisphosphonate, risedronate (Actonel, Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA) is available in 5 mg/day and 35 mg/week dosages. It works in a very similar way to alendronate and is licensed for the prevention and treatment of osteoporosis in postmenopausal women, to reduce vertebral and hip fractures. It has a license for GCIOP in its daily formulation and, similar to alendronate, is often used "off license" for this condition in its once-weekly form. The drug does not have a license for male osteoporosis, but it seems unlikely that it would be ineffective in this group of subjects. The same precautions for administration of risedronate should be adopted as for alendronate, to ensure minimal gastrointestinal side effects and maximum bioavailability. The major placebo-controlled trials of effectiveness for fracture reduction are the Vertebral Efficacy with Risedronate Therapy in North America (VERT-NA) and the rest of the world (VERT-MN). The former trial ran for 3 years and included nearly 2500 postmenopausal women who were younger than 85 years and had at least one vertebral fracture. Subjects were randomised to receive oral risedronate (2.5 or 5 mg/day) for 3 years or placebo. The 2.5 mg/day risedronate arm was discontinued after 1 year.

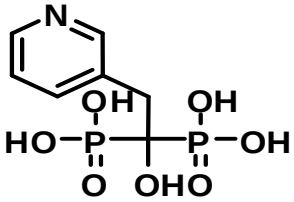

Figure 10. Structure of risedronate.

Ibandronate: The most recently developed bisphosphonate is ibandronate (Bonviva, Glaxo Smith Kline, Uxbridge, Middlesex, UK). The drug is licensed at an oral dose of 150 mg/month for the treatment of osteoporosis in postmenopausal women, to reduce the risk of vertebral fracture. Ibandronate is a third generation bisphosphonate, which inhibits bone resorption in the same way as the therapies outlined above. Administration advice is similar to that for risedronate and alendronate, but there is a requirement for the subject to spend a period of 1 hour upright before eating or drinking following administration. It is probable that this enhances bioavailability. The definitive evidence for ibandronate comes from the oral Ibandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) study, which employed a dosage of 2.5 mg/day compared with an equivalent intermittent regimen of 20 mg on alternate days for 12 doses every 3 months. This 3-year study involved nearly 3000 postmenopausal women who were aged 55–80 years and had a BMD T-score of 2.0 at any one lumbar vertebra and at least one prior vertebral fracture. Over 3 years there was a significant (62%; 95% CI, 40.9–75.1) reduction in morphometric vertebral fracture in the daily administered group, with a 50% (95% CI, 26–60) reduction in the intermittently administered group.

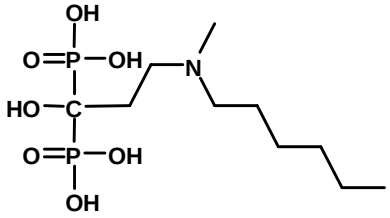

Figure 11. Structure of ibandronate.

Parathyroid Hormone (PTH; Teriparatide): A biologically active 34-amino acid synthetic peptide fragment of PTH (teriparatide; Forsteo, Eli Lilly Nederland B. V., Houten, Nederland) is licensed for the treatment of postmenopausal osteoporosis, although it also has approval for use in men in the USA. It is administered by daily subcutaneous injection and is supplied in a prefilled 3 ml syringe. The syringe volume contains 750 g, which is enough for 28 days of the licensed 20 g/day dosage regimen. The maximum length of treatment is 18 months. The mode of action differs fundamentally from the previously described preparations because it stimulates osteoblastic activity and cell survival, and, therefore, promotes an anabolic or bone-forming effect, most significantly in skeletal sites with a high proportion of trabecular bone. This has obvious possibilities in regaining lost bone mass and normalizing the microarchitecture. The definitive study was a randomized, placebo-controlled study (the Fracture Prevention Trial), involving 1637 postmenopausal women with existing vertebral fractures who were treated with 20 g/day or 40 g/day doses of teriparatide. The study was designed to last 3 years but was terminated at 18 months because of the occurrence of sarcoma in rats, even though these findings are not thought to be relevant to humans. Teriparatide significantly increased BMD in the lumbar spine and reduced the risk of new vertebral and non vertebral fractures. The authors reported RRs of vertebral fracture in the 20 g/day and 40 g/day ibandronate- treated groups as 0.35 and 0.31, respectively (95% CI, 0.22–0.55 and 0.19–0.50, respectively), compared with placebo. The RR of nonvertebral fragility fracture was 0.47 and 0.46, respectively (95% CI, 0.25–0.88 and 0.25–0.86, respectively). The incidence of new moderate and severe vertebral fractures (defined as a loss of height _26%) was even more effectively reduced, with a RR of 0.1 and 0.22, respectively (95% CI, 0.04–0.27 and 0.11–0.45, respectively). The ibandronate, 40 g/day dose increased BMD to a greater extent than the ibandronate, 20 g/day dose, although this was not reflected in the fracture outcomes and the higher dose was more likely to have side effects, which were similar to placebo at the ibandronate, 20 g/day dose,

consisting principally of nausea, dizziness, leg cramps, and headache.

Strontium Ranelate: Strontium ranelate (Protelos, Servier, Neuilly-sur-Seine, France) consists of two atoms of strontium and a molecule of ranelic acid, to ensure absorption. Strontium is in the same atomic group as calcium, which it replaces within bone. Protelos is a daily preparation of granules that are taken as a suspension (2 g in a glass of water) at least 2 hours after food, preferably at bed time. Strontium ranelate is licensed for the treatment of postmenopausal osteoporosis, to reduce the risk of both vertebral and hip fractures. However, the drug is not licensed for prevention of osteoporosis, use in men, or GCIOP. The drug seems to have a unique mode of action that is not fully understood but seems to uncouple bone turnover and involve both suppression of resorption, by inhibiting the differentiation of preosteoclasts into multicellular osteoclasts, and maintenance of bone formation, through enhanced collagen synthesis and osteoblast replication.[54,55] Although it is always important to differentiate between benefits on BMD and antifracture efficacy of any treatment for osteoporosis, this is even truer for strontium ranelate. Because the atomic weight of strontium is higher than that of calcium and, therefore, attenuates X-ray transmission to a greater extent, the apparent increase in BMD will be partly explained by the percentage of calcium atoms replaced by strontium atoms. Because this is likely to depend on the duration of and compliance with therapy, in addition to the ROI being scanned, it is difficult to define an adjustment factor without a measure of the bone's strontium content.

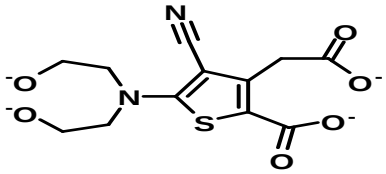

Figure 12. Strontium ranelate

Calcium and Vitamin D: There is a positive association between calcium intake and bone mass. Healthy bones need a balanced, calcium-rich diet throughout life. Lifelong inadequate dietary intake is associated with failure to achieve peak bone mass (PBM). Calcium and vitamin D supplementation has been shown to reduce the rate of bone loss in postmenopausal women and in those 65 years of age. In older women, both adequate levels of dietary calcium and calcium supplements had been thought to reduce fracture risk, with a dose-dependent relationship and these sort of findings support the recommendations in some guidelines for higher levels of calcium supplementation in women with osteoporosis than the usual recommended nutrient intake (RNI) of 700 mg/day for individuals of 65 years. Three more recent RCTs have failed to demonstrate, on an "intention-to-treat" basis, significant fracture reduction in community-living older people with calcium supplementation alone or in combination with vitamin D. Other large-scale observational studies in older women have also supported this view.

A meta analysis from the Cochrane Group recently reported no benefit on fracture outcomes in community-dwelling older people or in those treated with vitamin D alone. Compliance in the RCTs has been noted as a possible explanation for an apparent lack of effect, and an even more recent paper seemed to show a 34% reduction of fracture in approximately 700 compliant women out of just over 1400 subjects, who were 70 years, after 5 years of treatment. Whatever the controversies regarding the role of calcium, with or without vitamin D supplementation, in community-living older people, calcium (1200 mg/day) and vitamin D (800 IU/day) supplementation can be particularly important in the elderly in the residential and nursing home environment. This group has a much higher risk of hip fracture than community-living older people. Research carried out in women living in institutions in France has shown effectiveness and cost-effectiveness in preventing hip fracture, with a risk reduction of approximately 30%. It is not clear from these studies whether calcium or vitamin D, or a combination of the two, is the effective agent. It is possible that a primary benefit comes from the correction of vitamin D insufficiency, which is beneficial to falls risk through optimization of neuromuscular strength and coordination rather than through benefits to bone health.

Vitamin D consists of two similar molecules, vitamin D2 (ergocalciferol) and vitamin D3 (colecalciferol). It is absorbed in the gut and synthesized in the skin from a provitamin (7-dehydrocholesterol) under the influence of sunlight; for this reason, it is not, in fact, a vitamin, but is better described as "a steroid hormone". The confusion probably arose from the dramatic effect of cod liver oil supplementation in childhood rickets. Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D] and converted into its active form, 1,25- dihydroxyvitamin D [1,25(OH)2D], in the kidney. Vitamin D has not often been studied as an isolated pharmacological intervention for fracture. In a study based in Holland and involving community-living individuals, no effect on fracture was found at a dose of vitamin D, 400 IU/day.

Another study found that, even in the residential care environment, there was lack of significant benefit on fracture, although there was a significant reduction in falls if subjects were at least 50% compliant, even if they were not vitamin D-deficient at baseline. However, a metaanalysis of RCTs of vitamin D3 with or without calcium that had fracture as an outcome reported a RR reduction in ambulatory and institutionalized elderly persons of 26% (RR, 0.74; 95% CI, 0.61–0.68) at a dose of vitamin D3 of 700–800 IU/day. This effect disappeared at a dose of

vitamin D3 of 400 IU/day. One problem is that there is controversy regarding the serum levels of 25(OH)D that define insufficiency and deficiency and the daily intake of vitamin D necessary to maintain these levels. This is complicated because the majority of vitamin D is synthesized in the skin and this process becomes roughly 50% less efficient with ageing. Because of the difficulty of formulating a reasonably acceptable diet that will compensate, replacement therapy often becomes necessary. The RNI for vitamin D is 10 g/day (400 IU/day).

Calcitriol: Calcitriol or (OH)2D (Rocaltrol, Hoffman-La Roche, Nutley, NJ, USA) is licensed for the treatment of established postmenopausal osteoporosis. It is the active form of vitamin D, which is produced by renal hydroxylation of colecalciferol [25(OH)D]. Because of renal impairment in older people, there is a risk of inadequate levels of the active metabolite. Because vitamin D is essential to the maintenance of adequate bone health and deficiency is associated with hyperparathyroidism and low levels of BMD, calcitriol has been promoted as a treatment for established postmenopausal osteoporosis.

Calcitriol was compared with calcium in a single-blind study of just over 600 postmenopausal women with at least one prior vertebral fracture; there was a reduction in the rate of vertebral fracture over 3 years in the active treatment (Calcitriol) arm of the study. During the second year of treatment, there were 9.3 fractures per 100 subject years in the calcitriol group compared with 25.0 fractures per 100 subject years in the control group. In the third year, there were 9.9 per 100 subject years in the Calcitriol group compared with 31.5 fractures per 100 subject years in the control group (p 0.001). On this basis, the medication has a license and is used in some countries but has little of the market in the UK, perhaps because its use requires regular monitoring of serum calcium owing to of the rare occurrence of hypercalcaemia.

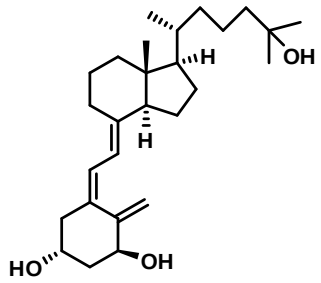

Figure 13. Structure of calcitriol.

Calcitonin: Calcitonin (Miacalcic, Sandoz International GmbH, Holzkirken, Germany) is available as an intramuscular or subcutaneous injection of 100 IU/day in one or two divided doses. The drug is licensed for acute bone loss associated with immobility for 2 to 4 weeks. Calcitonin seems to have some benefit in reducing pain from acute vertebral fracture, although this use is not supported by robust evidence or its license. The drug has a number of side effects, including flushing, nausea, and diarrhoea and should be used with caution in people with allergies. Hypocalcaemia can be a problem and this must be monitored. A nasal form of calcitonin is available, at a dose of 200 IU/day, to reduce the risk of vertebral fracture in postmenopausal osteoporosis. The Prevent Recurrence of Osteoporotic Fractures (PROOF) study examined the effect of 100 IU/day, 200 IU/day, and 400 IU/day of calcitonin in just over 1200 postmenopausal women with prior vertebral fracture and a T-score of 2.0 over 5 years. Only 132 of the 316 subjects assigned to the licensed dose of 200 IU/day completed the study. Of the 287 subjects that completed the 3-year study, there was a 35% reduction of new vertebral fracture (RR, 0.65; 95% CI, 0.47–0.97). Significant fracture reduction was not seen with any other dosage of calcitonin, including the highest dose. Apart from rhinitis, the drug was quite well tolerated. The high drop-out rate and the fact that there no dose-dependent effects were demonstrated means the study can be criticized. Calcitonin is now rarely used in clinical practice.

Nondrug Treatment Options: This chapter concentrates on the pharmacotherapeutic agents that are promoted to reduce fracture. It must be acknowledged that there is a close relationship between falls and fractures and the absolute risk of fracture following a fall could be between 3% and 5%; with between 20% and 25% of those falls resulting in hip fracture, these studies might underreport the true fall rate.[92,93] The combination of osteoporosis and a recent fall might amplify the fracture risk by a factor as high as 24.8. Although there is now robust evidence that certain interventions can reduce the rate of falling, it is very difficult to demonstrate that these interventions can reduce fracture, hospital admission, or nursing home admission because assessment and intervention are far more complex than those for 204 Jonathan R. Bayly osteoporosis and the subject numbers needed for a trial powerful enough to show benefit would be unfeasibly large. Nevertheless, on a pragmatic basis, interventions that reduce the rate of falling and the number of individuals who fall might integrate well with strategies designed to improve bone health. Hip protectors were once considered an effective strategy for fracture reduction, and, indeed, they can be, if worn at the time of the fall. Compliance, however, is a major problem, and on an "intention-to-treat" basis, recent trials involving individual subject randomization have failed to demonstrate a benefit, except possibly within the care home environment.[96]

Conclusion

There is now clear evidence from large, well-designed RCTs for effective and worthwhile interventions to reduce the risk of further fractures in subjects who are replete in calcium and vitamin D. In the context of financial constraints in healthcare economics, it is essential to ensure cost-effective prescribing so that

only subjects at high risk receive appropriate therapies. These are often the older and less articulate subjects, and opportunistic case finding, as opposed to a systematic approach to care, runs the risk of inequality of access. There is consistent and repeatable evidence that our present approach is failing to identify or appropriately manage the overwhelming majority of even the highest risk subjects, such as those with prior fragility fracture, as described above, or those who are receiving glucocorticoids97 or who are resident in the extended care setting. 98 Not only do these issues need urgent attention, but also systems are needed to improve the poor concordance and persistence with treatments for osteoporosis.

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