

Osteoporosis: now and the future

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Osteoporosis is a common disease characterised by a systemic impairment of bone mass and microarchitecture that results in fragility fractures. With an ageing population, the medical and socioeconomic effect of osteoporosis, particularly postmenopausal osteoporosis, will increase further. A detailed knowledge of bone biology with molecular insights into the communication between bone-forming osteoblasts and bone-resorbing osteoclasts and the orchestrating signalling network has led to the identification of novel therapeutic targets. Novel treatment strategies have been developed that aim to inhibit excessive bone resorption and increase bone formation. The most promising novel treatments include: denosumab, a monoclonal antibody for receptor activator of NF- κ B ligand, a key osteoclast cytokine; odanacatib, a specific inhibitor of the osteoclast protease cathepsin K; and antibodies against the proteins sclerostin and dickkopf-1, two endogenous inhibitors of bone formation. This overview discusses these novel therapies and explains their underlying physiology.

Introduction

Osteoporosis is an emerging medical and socioeconomic threat characterised by a systemic impairment of bone mass, strength, and microarchitecture, which increases the propensity of fragility fractures (figure 1).¹ Bone-mineral density (BMD) can be assessed with dual x-ray absorptiometry (DXA), and osteoporosis is defined by a T score of less than 2.5, ie, more than 2.5 standard deviations below the average of a young adult. About 40% of white postmenopausal women are affected by osteoporosis and, with an ageing population, this number is expected to steadily increase in the near future.^{2–4} The lifetime fracture risk of a patient with osteoporosis is as high as 40%, and fractures most commonly occur in the spine, hip, or wrist (figure 1), but other bones such as the trochanter, humerus, or ribs can also be affected. From a patient's perspective, a fracture and the subsequent loss of mobility and autonomy often represent a major drop in quality of life. Additionally, osteoporotic fractures of the hip and spine carry a 12-month excess mortality of up to 20%, because they require hospitalisation and they have subsequently enhanced risk of other complications, such as pneumonia or thromboembolic disease due to chronic immobilisation (panel 1).⁵

A high index of suspicion is needed for early diagnosis of osteoporosis because elderly patients can concurrently have other comorbidities that receive more attention, such as cardiovascular diseases or cancer.

Because bone loss occurs insidiously and is initially asymptomatic, osteoporosis is often only diagnosed after the first clinical fracture has occurred.^{6,7} Consequently, the aim of therapy is usually prevention of further fractures. Early assessment of an individual's risk of osteoporosis is therefore important to prevent the first fracture. National and international guidelines have been implemented to address the challenge of screening for osteoporosis in an evidence-based and cost-effective manner.^{8–10} Several risk factors, such as age, low body-mass index, previous fragility fractures, a family history of fractures, the use of glucocorticoids, and active cigarette smoking have to be taken into account.¹¹ The measurement of BMD by DXA is a valid method to diagnose osteoporosis and to predict the risk of fracture.¹² New decision-making methods, such as the fracture-risk assessment tool (FRAX), have integrated clinical risk factors with DXA-based BMD to predict an individual's 10-year risk of sustaining a hip fracture as well as the 10-year probability of having a major osteoporotic fracture, defined as clinical spine, forearm, hip, or shoulder fracture.⁶ Panel 2 shows an example of how to use BMD and clinical risk factors within the FRAX model to guide decisions for osteoporosis treatment. Although the baseline characteristics of all three patients are similar with regards to body-mass index and BMD, their risk profiles and ensuing risk of having a fracture in the next 10 years varies greatly. This model underlines the importance of considering additional individual risk factors and comorbidities in osteoporosis management.

Although DXA is widely available and has been commonly used for clinical phase-3 studies, it has some limitations. As an area-based measure of bone mineral, DXA does not allow assessment of bone geometry, neither does it distinguish between cortical bone, the outer shell, and trabecular bone, the spongy inner part, which are important determinants of bone strength and loss at different rates. Advances in imaging techniques with high-resolution peripheral CT that yield volumetric bone-density data might allow better prediction of bone strength and thus fracture risk, if indices such as

Search strategy and criteria

We searched Medline and PubMed for articles published between 2000 and 2010. We used the search terms "osteoporosis" in combination with "treatment", "RANK ligand", "denosumab", "cathepsin K", "odanacatib", "saracatinib", "calcium-sensing receptor", "calcilytic", "sclerostin", and "dickkopf-1". We largely selected original papers and reviews published in the past 5 years, but did not exclude commonly referenced and important older publications. We also searched the ClinicalTrials.gov database for clinical trials. We focused on randomised trials and meta-analyses, if available. We also analysed the reference sections of identified articles for relevant papers. Recent review articles are cited to provide readers with detailed information. We added selected references as recommended during the peer-review process.

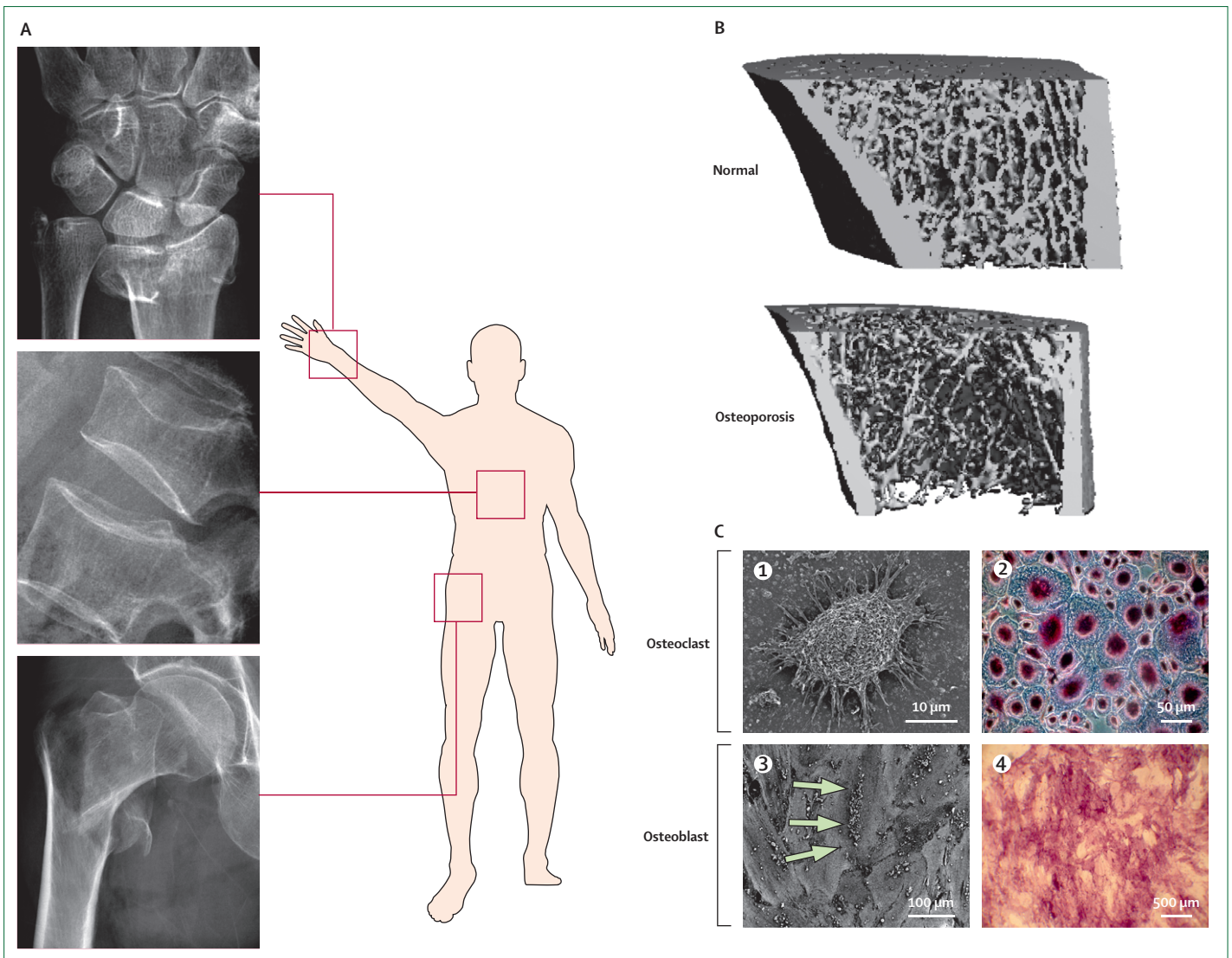


Figure 1: Osteoporosis at a glance

Osteoporosis is a systemic skeletal disease in which bone resorption exceeds bone formation and results in microarchitectural changes. (A) Fragility fractures typically involve wrist, vertebrae, and hip. (B) Microcomputed tomography shows marked trabecular thinning of osteoporotic bone compared with normal bone. (C) Microscopic views of bone-resorbing osteoclasts and bone-forming osteoblasts: (1) osteoclast with its distinctive morphology; (2) tartrate-resistant acidic phosphatase staining of multinucleated osteoclasts; (3) multiple osteoblasts (white arrowheads) on mineralised matrix; (4) alkaline phosphatase staining of osteoblasts.

intracortical porosity are taken into account.¹³ Whether these novel techniques will be useful in daily practice remains to be seen.

Current therapies

In addition to lifestyle modifications (cessation of smoking, reduction of alcohol consumption, and increased physical activity), vitamin D and calcium supplementation is recommended as baseline treatment in every patient with osteoporosis. The efficacy of specific osteoporosis drugs has only been shown if these supplements were concurrently given. Use of vitamin D as a drug has had a renaissance because vitamin-D

deficiency is highly prevalent and associated with various adverse extraskeletal effects, including cardiovascular and metabolic diseases, malignancies, and a high propensity to falls.¹⁴ Serum concentrations of 25-hydroxy-vitamin D of at least 30 ng/mL are the target, which usually requires a dose of vitamin D of at least 800 IU per day. A meta-analysis¹⁵ raised concerns that calcium supplementation could be associated with an increased risk of cardiovascular events.¹⁵ The risk of having a myocardial infarction was 27% higher in individuals receiving at least 500 mg per day of calcium supplementation than in those not receiving calcium supplementation on the basis of 11 trials that included

Panel 1: Key points of burden of osteoporosis

- Characterised by insidious loss of bone mass and strength
- Typically associated with vertebral, hip, intertrochanteric, proximal humerus, and wrist fractures
- Results in chronic pain, loss of autonomy, and increased mortality
- DXA measurement is accurate and valid method for early diagnosis
- Present therapies are efficient, but have poor long-term adherence

almost 11921 patients. As a caveat, only studies with calcium supplementation but no vitamin-D supplementation were included. Therefore concurrent vitamin-D deficiency could have been present, which itself increases the risk of cardiovascular events.¹⁴ The Women's Health Initiative showed that calcium in combination with vitamin D had no effect on the risk of coronary heart disease, which is reassuring in this regard.¹⁶ Nonetheless, the American Society for Bone and Mineral Research has issued a statement and recommends the use of combined vitamin D and calcium supplementation instead of only-calcium supplementation, and the preference for an increased dietary uptake of calcium over calcium supplements.

Osteoporosis therapies fall into two classes, anti-resorptive drugs, which slow down bone resorption, and anabolic drugs, which stimulate bone formation. Currently, several approved treatment options exist for the management of osteoporosis that effectively reduce the risk of vertebral, non-vertebral, and hip fractures (table 2).¹⁷⁻²⁷ In fact, clear evidence of reduction of the risk of vertebral fracture is a requirement for any novel osteoporotic drug to be registered. Of the antiresorptive drugs, bisphosphonates, with their high affinity for bone and long safety record, constitute the largest class. Bisphosphonates can be given orally or intravenously, and are most widely used because they can be inexpensive and used across a broad spectrum of osteoporosis types, including postmenopausal, male, and steroid-induced osteoporosis, as well as Paget's disease. Other anti-resorptive drugs, such as raloxifene, strontium ranelate, and most recently, denosumab, can be alternatives for women with postmenopausal osteoporosis. Bone-anabolic drugs that build up new bone, rather than preventing its loss, are limited to the full-length parathyroid hormone (PTH 1-84) or its N-terminal fragment, teriparatide (PTH 1-34). Both are given subcutaneously, but transdermal forms of PTH 1-34 are in development.²⁸

Although these drugs are effective, most have some limitations and side-effects that affect long-term administration and adherence (table 2).²⁹ For a more detailed overview of the different treatments for osteoporosis, we recommend a recent review.³⁰ Here we summarise the recent progress in bone biology that has

Panel 2: Example of management of osteoporosis with FRAX method for risk assessment and guidelines

Three postmenopausal women from the UK present for assessment of osteoporosis treatment after DXA measurement of femoral neck revealed T score of -2.6 (table 1). Their height is 170 cm, weight 55 kg, and body-mass index 19 kg/m². None smokes currently, takes systemic glucocorticoids, has rheumatoid arthritis or secondary osteoporosis, or consumes excessive amounts of alcohol.

	Anne	Betty	Charlotte
Age (years)	70	60	80
Previous fracture	No	Yes	Yes
Parent fractured hip	No	Yes	Yes
10-year risk of fracture (%)			
Major osteoporotic fracture	12	25	36
Hip fracture	3.7	4.8	27

Table 1: Characteristics of three postmenopausal women

- Anne has no additional risk factors to her low bone-mineral density. According to FRAX tool, she has 10-year fracture risk of getting major osteoporotic fracture of 12% and risk of getting hip fracture of 3.7%. Lifestyle advice, reassurance, and supplementation with vitamin D or calcium would suffice, but she would not receive specific osteoporosis treatment. Repeat DXA scan after 5 years is recommended.
- Although Betty is 10 years younger, her positive family history and previous fracture puts her at greater risk of getting osteoporotic fracture. She would receive specific osteoporosis treatment.
- Charlotte has similar risk profile to Betty but is 20 years older. This alone suffices to increase her hip fracture risk by more than five times.

defined novel drugs and show how this progress could translate into future osteoporosis treatments.

Recent developments in bone biology

In the past decade, the pathogenesis of osteoporosis has been linked to tissue, cellular, and molecular processes (figure 1). Master signals that integrate various endocrine, neuroendocrine, inflammatory, and mechanical stimuli have been defined. At the cellular level, communication and coupling between the main bone-cell types, the bone-forming osteoblasts and the bone-degrading osteoclasts, constitute the smallest functional unit (figure 1). Several key molecules coordinate activities of osteoblasts and osteoclasts during bone remodelling. Detailed knowledge of the molecular and cellular players has created a new concept in bone pathophysiology. With some of these new principles finding their way into clinical practice, we highlight the most relevant advances.

For more on the American Society for Bone and Mineral Research see <http://www.asbmr.org>

	Dose	Interval	Route	Efficacy against		Side-effects
				Hip fractures	Vertebral fractures	
Bisphosphonates						
Alendronate	70 mg	Weekly	Oral	Black ¹³	Cummings ¹⁴	Osteonecrosis of the jaw, subtrochanteric femur fractures
Risedronate	35 mg or 150 mg	Weekly or monthly	Oral	McClung ¹⁵	Harris ¹⁶	Oesophageal irritation
Ibandronate	150 mg	Monthly	Oral	No data	Chesnut ¹⁷	Oesophageal irritation
Ibandronate	3 mg	Every 3 months	IV	No data available	No data available	Acute-phase reaction
Zoledronic acid	5 mg	Yearly	IV	Black ¹⁸	Black ¹⁸	Acute-phase reaction, hypocalcaemia, potential renal toxic effects
Raloxifene	60 mg	Daily	Oral	No effect	Delmas ¹⁹	Thromboembolic disease
Strontium ranelate*	2 g	Daily	Oral	Reginster ²⁰	Meunier ²¹	Thromboembolic disease; drug rash with eosinophilia systemic syndrome, abdominal discomfort
Teriparatide	20 µg	Daily	SC	No effect	Neer ²²	Hypercalcaemia, nausea, diarrhoea
PTH (1-84)‡	100 µg	Daily	SC	No effect	Greenspan ²³	Hypercalcaemia, nausea, diarrhoea

Drugs that reduce the risk of vertebral (and hip) fractures when used with adequate calcium and vitamin-D supplementation. IV=intravenous. SC=subcutaneous. APR=acute-phase reaction. *Approved in more than 70 countries, but not USA. ‡Approved in Europe but not USA.

Table 2: Established treatments for osteoporosis

Osteoclasts and bone resorption

Osteoclasts originate from haemopoietic stem cells and are closely related to monocytes and macrophages (figures 1 and 2). Differentiation from osteoclast precursor to fully activated multinucleated osteoclast depends essentially on receptor activator of NF-κB ligand (RANKL), a member of the tumour necrosis factor (TNF) family, and the permissive role of macrophage-colony-stimulating factor (M-CSF). RANKL, abundantly expressed by bone-forming osteoblasts, bone-marrow stromal cells, and T and B lymphocytes, activates its receptor, RANK, expressed on osteoclasts. After RANKL-induced RANK stimulation, several key regulatory transcription factors and enzymes are induced to promote the differentiation, proliferation, multinucleation, activation, and survival of osteoclasts. The result is profound resorption of bone. Of note, mice with deletion of RANKL or RANK lack mature osteoclasts.³¹ Osteoprotegerin (OPG) is a naturally occurring antagonist of RANKL.³² In early menopause, the acute phase of oestrogen deficiency, RANKL expression by bone-marrow stromal cells and lymphocytes increases and is associated with enhanced bone loss.³³ In addition to menopause, conditions in which suppression of sex hormones is therapeutically induced (eg, in men with prostate cancer or in women with receptor-positive breast cancer), are also associated with an activated RANKL/RANK pathway and enhanced bone resorption. Various hormones^{34,35} and inflammatory cytokines³⁶ modulate osteoclast biology through the RANKL pathway. Additionally, immunological and malignant bone disorders that destroy bone locally are associated with high RANKL activity, including rheumatoid arthritis,³⁷ periodontal disease,³⁸ myeloma bone disease,³⁹ and osteolytic bone metastasis.⁴⁰

The src kinase is highly expressed in osteoclasts and mediates multiple pathways regulating osteoclast activity. Src-deficient mice have osteopetrosis because their osteoclasts do not have an intact ruffled border.^{41,42} Interestingly, the absence of src does not alter the number of osteoclasts⁴² and is associated with an enhanced rate of osteoblastic bone formation.⁴³ With their jelly-fish-like shape, motile cytoskeleton, and adhesion molecules such as integrins (figure 2), osteoclasts attach to bone and create a sealing zone on the bone surface, which provides a highly enriched acidic microenvironment. Cathepsin K is a key cysteine proteinase of the mature osteoclast that degrades collagen and breaks down bone. Cathepsin K is a crucial determinant of resorptive activity by osteoclasts; bone of poor quality in which microcracks have accumulated is removed, and hole-like lacunae appear. Thus people without functioning cathepsin K have pycnodysostosis, a rare disease characterised by osteosclerosis, a dense, but brittle bone phenotype, short stature, and lytic lesions of the distal phalanges because of poorly functioning osteoclasts.⁴⁴ A more severe phenotype, osteopetrosis (so-called marble bone disease) has been described in cathepsin K-deficient mice.⁴⁵

Osteoblasts and bone formation

The osteoblast is a unique bone-forming cell derived from mesenchymal stem cells (figures 1 and 3). The rate of bone formation is determined by the speed and effectiveness of precursor cells differentiating into mature osteoblasts which secrete matrix that can be mineralised and by their life span. These processes are enhanced by vitamin D as well as by intermittent pulses of parathyroid hormone, a treatment scheme used by daily injections of teriparatide. By contrast, bone formation can be suppressed by exogenous glucocorticoids or be impaired in

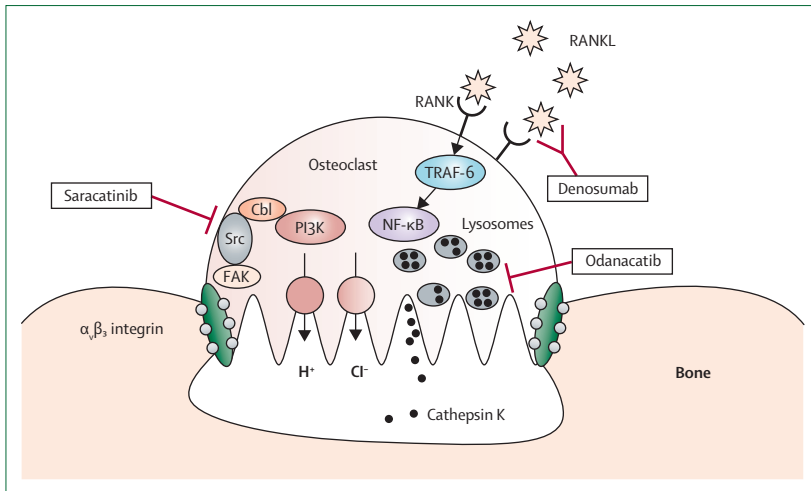


Figure 2: Osteoclast physiology and potential therapeutic targets
 With help of $\alpha_2\beta_1$ integrin, osteoclast attaches to bone surface and forms sealing zone. Proton pumps and chloride channels produce highly acidic microenvironment that is essential for catalytic activity of osteoclastic enzymes such as cathepsin K. Odanacatib inhibits cathepsin K, a lysosomal protease that degrades collagens. Tyrosine src kinase has crucial role in osteoclast activity and can be inhibited by saracatinib. RANKL acts as essential regulator of osteoclast differentiation and activity. Fully human monoclonal antibody denosumab prevents RANKL binding to its receptor RANK. FAK=focal adhesion kinase. NF- κ B=nuclear factor kappa B. PI3K=phosphatidylinositol 3-kinase. RANK=receptor activator of NF- κ B. RANKL=RANK ligand. TRAF-6=tumour necrosis factor receptor associated factor 6.

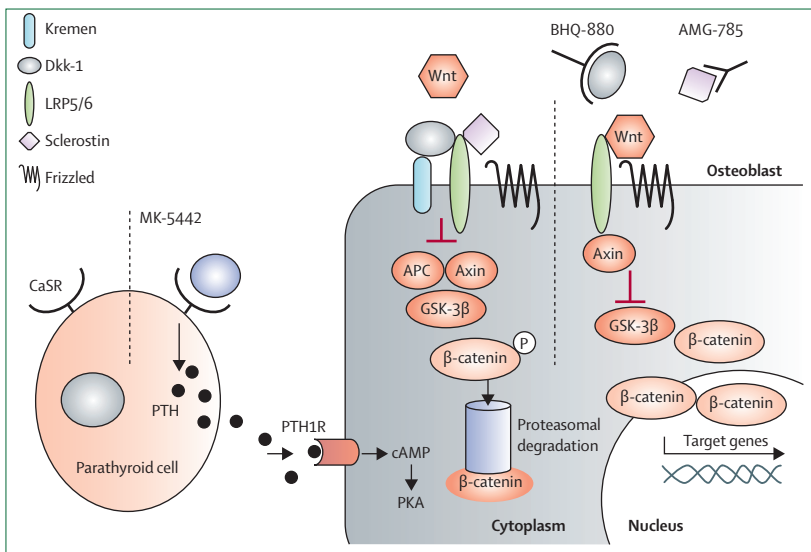


Figure 3: Osteoblast physiology and potential therapeutic targets
 Calcium-sensing receptor is antagonised by MK-5442 and triggers short bursts of PTH secretion. Binding of PTH to its receptor enhances osteoblast functions and bone formation. Presence of Wnt antagonists Dkk-1 and sclerostin inhibits Wnt signalling. Dkk-1 needs to form complex with Kremen to bind LRP5/6, whereas sclerostin binds LRP5/6 directly. BHQ-880 and AMG-785 are antibodies for Dkk-1 and sclerostin, respectively. After neutralising Dkk-1 and sclerostin, Wnt can bind to LRP5/6, which results in degradation GSK-3 β . As a consequence, β -catenin is stabilised, accumulates, and translocates into the nucleus where it regulates transcription of osteoblastic genes. APC=adenomatous polyposis coli. cAMP=cyclic adenosine monophosphate. CaSR=calcium sensing receptor. Dkk-1=dickkopf-1. GSK=glycogen synthase kinase 3. LRP=low-density lipoprotein receptor-related protein. PKA=protein kinase A. PTH=parathyroid hormone. PTH1R=PTH 1 receptor.

some elderly patients. At sites of resorption lacunae, a team of osteoblasts produces an extracellular matrix containing type-1 collagen and various non-collagenous proteins, such as osteocalcin, osteonectin, osteopontin,

and others. Vitamin D, calcium, and phosphate help this matrix mineralise.

The calcium-sensing receptor (CaSR) on the parathyroid gland controls PTH release to maintain serum calcium concentrations within a narrow physiological range. Whereas hypocalcaemia stimulates the CaSR and release of PTH to increase serum calcium, hypercalcaemia has the opposite effects.⁴⁶ Accordingly, drugs that mimic high concentrations of calcium at the CaSR and suppress PTH secretion are termed calcimimetic drugs (eg, cinacalcet), whereas drugs that mimic low concentrations of calcium are termed calcilytic drugs (eg, MK-5442).⁴⁷ Although the physiological role of the CaSR expressed on osteoblasts and osteoclasts is not fully understood, it might mediate some of the effects of the osteoporosis drug strontium ranelate (table 2).⁴⁸

At the molecular level, activation of the canonical Wnt/ β -catenin pathway is the master switch for osteoblastic differentiation.⁴⁹ This key bone-anabolic pathway is negatively regulated by Wnt inhibitors such as dickkopf-1 (Dkk-1) and sclerostin, which bind and block the Wnt receptor LRP-5 (figure 3).⁵⁰

Osteocytes

Osteocytes account for more than 90% of all bone cells and are found scattered throughout the mineralised matrix. They are terminally differentiated osteoblasts and share morphological similarities with neural cells. Their long dendritic processes form a sensory network, whereby they can sense and communicate mechanical stress within the bone. Osteocytes also express several factors known to regulate phosphate metabolism, which suggests a role in matrix mineralisation. Additionally, osteocytes exclusively produce and secrete sclerostin,⁵¹ an inhibitor of the Wnt-signalling pathway, which inhibits osteoblast differentiation and bone formation.

Novel targets for treatment of osteoporosis

Antiresorptive therapies

Denosumab

The prominent role of RANKL in osteoclastogenesis has made it a prime target in diseases characterised by excessive bone loss (table 3). Initially, a chimeric OPG-Fc fusion protein was used to antagonise RANKL.⁵² However, the formation of neutralising antibodies against OPG after administration of the fusion protein, and its potential cross-reactivity with tumour-necrosis-factor-related apoptosis-inducing ligand (TRAIL),⁵³ led to a new strategy; the development of denosumab, a fully human monoclonal antibody against RANKL. Denosumab displays a higher specificity and affinity for RANKL with superior pharmacokinetic properties compared with OPG-Fc, translating into a longer dosing interval of 6 months.⁵⁴ A large study programme on a wide range of bone diseases, including several types of osteoporosis⁵⁴⁻⁶⁰ and bone metastases, is ongoing.⁶¹ With completed phase-3 studies, denosumab is the most advanced of all

	Target (function)	Drug class	Phase	Route
Antiresorptive drugs				
Denosumab*	RANK ligand (stem-cell factor for osteoclasts)	Antibody against RANKL	3 (completed)	SC
Odanacatib	Cathepsin K (osteoclastic enzyme that degrades collagens)	Cathepsin K inhibitor	3	PO
Saracatinib	c-src kinase (enzyme involved in osteoclast activation)	c-src inhibitor	2	PO
Anabolic drugs				
MK-5442	CaSR (triggers PTH release if inhibited)	Calcilytic drug	2	PO
AMG 785	Sclerostin (inhibitor of the Wnt/ β -catenin pathway)	Antibody against sclerostin	2	SC
BHQ 880	Dickkopf-1 (inhibitor of the Wnt/ β -catenin pathway)	Antibody against dickkopf-1	1-2	SC

SC=subcutaneous. PO=per os. CaSR=calcium-sensing receptor. *Approved in Europe and USA in May/June, 2010.

Table 3: Clinical development of novel treatments for osteoporosis

investigational compounds and has recently been approved in Europe for osteoporosis and in the USA for osteoporosis and bone metastases.

In the phase-1 study,⁵⁴ one subcutaneous injection of denosumab suppressed, in a dose-dependent manner, urinary N-terminal telopeptide of type-1 collagen (NTX), a biochemical marker of bone resorption, by up to 81% in postmenopausal women for as long as 6 months and was well tolerated (table 4). Subsequently, a phase-2 study⁵⁵ with different doses (6–210 mg) and intervals (of 3–6 months) aimed to assess the effects of denosumab on BMD after 12 months in postmenopausal women with low bone-mass. A dose-dependent suppression of bone turnover was seen, with a decrease of the bone-resorption marker serum C-terminal telopeptide of type-1 collagen (CTX) as early as 3 days after administration of the drug and a maximum reduction of 88% in the groups given denosumab.

Denosumab increased BMD in the lumbar spine (range 3.0–6.7%), whereas women given placebo lost BMD of 0.8% in this period. At the total hip, BMD increased by 1.9–3.6% in the denosumab group, but decreased by 0.6% in the placebo group. The optimum dosing regimen for denosumab turned out to be 60 mg every 6 months. Extension of this study for another 12 months showed a sustained positive effect of denosumab on BMD at the lumbar spine, total hip, and the distal third of the radius.⁵⁶ Overall, treatment with denosumab was well tolerated and not associated with increased serious adverse events when compared with placebo. Of note, discontinuation of denosumab treatment caused a rapid increase of bone-turnover markers to values above baseline and even greater than those observed in the placebo group. Subsequently, serum concentrations of CTX returned to near baseline values and, after the patients were 24 months off treatment, were similar to concentrations in the placebo group.⁵⁷ Bone histomorphometry of patients from this study revealed absent osteoclasts in more than 50% of biopsy samples in the denosumab group. Bone turnover and bone formation were reduced in the denosumab group: 19% of patients given denosumab had tetracycline labelling of trabecular bone compared with 94% of

patients given placebo.⁵⁸ Long-term follow-up is needed to determine the clinical effects of suppressed bone turnover during denosumab treatment. The fast reversibility of denosumab on bone remodelling is ambiguous. Prolonged suppression of bone turnover did not occur after cessation of administration of denosumab. However, the rapid increase of bone turnover markers, starting 6 months after the last denosumab injection, has two practical implications: the need for a reliable recall-system to remind the patient about the next injection and, in case of discontinuation, of a follow-up strategy with another antiosteoporosis drug.

In a pivotal randomised placebo-controlled phase-3 study (FREEDOM),⁵⁹ denosumab (60 mg every 6 months) was assessed for its fracture reduction in 7868 women with postmenopausal osteoporosis, of whom 24% had pre-existing vertebral fractures. After 3 years, denosumab had reduced the risk of new radiographical vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20%. Of note, the risk of cardiovascular events, cancer, and infections did not differ between the two groups. However, the incidence of eczema (3.0% vs 1.7%) and cellulitis including erysipelas (0.3% vs <0.1%) was significantly higher in women given denosumab than in those given placebo.⁵⁹ No unusual pathogens were identified and all infections responded properly to standard antibiotics. Comprehensive assessment of the immune status of patients who were given denosumab for 12 months showed no relevant changes in white-cell count or in T-cell, B-cell, or NK-cell numbers.⁶⁵ In the follow-up of the FREEDOM cohort, one woman developed osteonecrosis of the jaw after dental extraction. Osteonecrosis of the jaw has been previously described as a rare complication with a frequency ranging from one in 100 000 to one in 10 000 patients treated for osteoporosis with bisphosphonates.⁶⁶

Two randomised placebo-controlled phase-3 studies have embarked on the use of denosumab in treatment-related osteoporosis: women receiving aromatase inhibitors for breast cancer⁶³ and men on androgen-ablation therapy for prostate cancer.⁶⁴ In both cases, sex hormone ablation is therapeutically intended to prolong disease-free survival but can commonly causes rapid

	Phase	n	Primary endpoint	Main results	Reference
Denosumab					
Single-dose placebo-controlled study in postmenopausal women	1	49	Biochemical markers of bone resorption after 6 months vs placebo	Urinary NTX decreased by 81% (3 mg/kg denosumab) vs -10% with placebo (p<0.001)	Bekker ⁵⁰
Efficacy and safety in postmenopausal women with low BMD	2	412	Percentage change from baseline BMD at lumbar spine after 12 months vs placebo	Lumbar spine BMD +3.0% to +6.7% vs -0.6% with placebo (p<0.001)	McClung ⁵¹
Treatment of postmenopausal osteoporosis (FREEDOM)	3	7868	Reduction of new vertebral fractures after 36 months vs placebo	Vertebral fractures decreased by 68% (RR 0.32, 95% CI 0.26-0.41); hip fractures decreased by 40% (RR 0.60, 95% CI 0.37-0.97)	Cummings ⁵⁵
Prevention of postmenopausal osteoporosis	3	332	Percentage change from baseline BMD at lumbar spine after 24 months vs placebo	Lumbar spine BMD +6.5% vs -0.6% with placebo (p<0.001)	Bone ⁵⁷
Comparison with alendronate in postmenopausal women with low BMD (DECIDE)	3	1189	Percentage change from baseline BMD at the total hip after 12 months vs alendronate	Total hip BMD +3.5% vs +2.6% with alendronate (p<0.0001)	Brown ⁵⁶
Treatment of bone loss in men on androgen-deprivation treatment for non-metastatic prostate cancer (HALT)	3	1468	Percentage change from baseline BMD at lumbar spine after 24 months	Lumbar spine BMD +5.6% vs -1.0 with placebo (p<0.001); after 36 months, vertebral fractures decreased by 62% (RR 0.38; 95% CI 0.19-0.78)	Smith ⁶¹
Treatment of bone loss in women on aromatase inhibitors for non-metastatic breast cancer	3	252	Percentage change from baseline BMD at lumbar spine after 12 months	Lumbar spine BMD +5.5% vs placebo (p<0.0001)	Ellis ⁶⁰
Odanacatib					
Multiple oral doses in healthy adults and once-weekly doses in healthy adult women	1	62; 78	Safety and tolerability	No increase in adverse events; serum CTX decreased by 62% (50 or 100 mg per week); BSAP and osteocalcin remained unaffected	Stoch ⁶²
Treatment of postmenopausal osteoporosis	2	399	Percentage change from baseline BMD at lumbar spine after 24 months	Lumbar spine BMD +5.5% vs -0.2% with placebo	Bone ⁶³
Treatment of postmenopausal osteoporosis	3	16 716	Vertebral, hip, and clinical non-clinical fractures after 36 months	Expected to be completed in July 2012	NCT00529373
ONO-5334					
Postmenopausal women with low BMD	2	265	Percentage change from baseline BMD at lumbar spine after 12 months	Completed in October 2009, results pending	NCT 00532337
Saracatinib					
Multiple oral doses on bone turnover in healthy men	1	59	Effect on bone turnover of multiple daily oral dosing for up to 24 days	Serum CTX -88% (95% CI 84-91%) vs +17% with placebo (p<0.001); PINP +13 vs +17% with placebo (p=NS)	Hannon ⁶⁴
MK-5442 (calcilytic drug)					
Dose-ranging study in postmenopausal osteoporosis	2	384	Percentage change from baseline BMD at lumbar spine after 12 months	Expected to be completed in February, 2012	NCT00960934
Postmenopausal osteoporosis previously treated with alendronate	2	480	Percentage change from baseline BMD at lumbar spine vs alendronate after 12 months	Expected to be completed in August, 2012	NCT00996801
AMG 785 (antibody for sclerostin)					
Healthy men and postmenopausal women	1	74	Safety	No increase in adverse events; after 21 days 3 mg/kg increased PINP, osteocalcin, and BSAP by 60-100%	NCT01059435
Postmenopausal women with low BMD (vs alendronate and teriparatide)	2	419	Percentage change from baseline BMD at lumbar spine after 12 months	Expected to be completed in August, 2012	NCT00896532
BHQ 880 (antibody against dickkopf-1)					
Combination with zoledronic acid in relapsed or refractory myeloma patients	1-2	267	Time to skeletal-related event; changes in bone resorption and formation markers after 9 months	Expected to be completed in April, 2012	NCT00741377

NTX=N-terminal telopeptide of type 1 collagen. BMD=bone-mineral density. RR=relative risk. CTX=C-terminal telopeptide of type 1 collagen. BSAP=bone-specific alkaline phosphatase. PINP=serum procollagen propeptide of type 1 collagen.

Table 4: Study programmes of investigational osteoporosis drugs

bone loss and fragility fractures. In women on aromatase inhibitors for non-metastatic breast cancer, denosumab (60 mg every 6 months for 12 months) increased BMD at the lumbar spine by 5.5% compared with placebo and was similarly effective regardless of the duration of aromatase inhibitor therapy.⁶³ However, this study was

not designed to assess fracture reduction. In the HALT study,⁶⁴ men under androgen deprivation therapy for prostate cancer were assessed. In this study, denosumab (60 mg every 6 months for 24 months) also increased BMD over 24 months at the lumbar spine by 6.7%, total hip by 4.8%, and distal third of the radius by 5.5%

compared with placebo.⁶⁴ Denosumab reduced the incidence of new vertebral fractures by 62% at 36 months compared with placebo (1·5% vs 3·9%). Serious side-effects were similar between denosumab and placebo, including cancers, infections, and cardiovascular events. Cataracts developed in more men given denosumab (4·7%) than in those given placebo (1·2%).

Denosumab is a novel and effective antiresorptive treatment for various metabolic bone diseases. Although direct comparative studies with fracture endpoints are not available for osteoporosis, completed trials with established surrogates suggest that the drug could be as effective as the most potent of the amino-bisphosphonates, zoledronic acid. Denosumab can be considered as a first-line treatment. Additionally, it can be given as an alternative to intravenous bisphosphonates, or if oral bisphosphonates are not tolerated (panel 3).

Several important characteristics clearly separate denosumab from bisphosphonates: (1) reversibility, because it targets RANKL and is not incorporated into the bone mineral, (2) lack of gastrointestinal side-effects and convenient biannual subcutaneous administration that could translate into improved long-term adherence, and (3) potential use in impaired renal function because of non-elimination by the kidneys. Although the dose does not have to be adjusted in patients with renal impairment, patients with severe renal impairment (creatinine clearance <30 mL/min) or on chronic haemodialysis are at greater risk of developing hypocalcaemia.

To minimise the risk of osteonecrosis of the jaw, patients who are scheduled to receive denosumab should be seen by a dentist if they have additional systemic (glucocorticoid therapy, chemotherapy) or local risk factors (radiation, dental diseases). In addition to recommending improved dental hygiene, invasive dental procedures should be avoided during denosumab treatment.

Odanacatib

On the basis of the concept that the protease cathepsin K has an important role in enzymatic bone degradation, the use of cathepsin-K inhibitors has emerged as a novel therapeutic approach. A high specificity and affinity for cathepsin K over other cathepsins (B, L, and S) that are widely expressed, particularly in the skin, was crucial for this class of compound.⁶⁷ Odanacatib is currently the most advanced inhibitor of cathepsin K under clinical investigation. Programmes with less specific cathepsin-K inhibitors were stopped because of cutaneous side-effects, such as a scleroderma-like skin thickening and rashes.^{67,68} In phase-1 studies, odanacatib at oral doses of 50 mg and 100 mg once a week reduced serum concentrations of the bone resorption marker CTX by 62%.⁶⁹ Daily administration of odanacatib (10 mg) reduced serum concentrations of CTX by 81%.⁶⁹

In a phase-2 study,⁷⁰ the effects of weekly oral doses of odanacatib were assessed in 399 women with postmenopausal osteoporosis. After 24 months, odanacatib

(50 mg) increased BMD in the lumbar spine by 5·7% and total hip by 4·1% compared with placebo. Bone-resorption markers were dose-dependently suppressed. Of note, a subset of 32 women undergoing bone biopsies followed by histomorphometry showed that treatment with odanacatib resulted in a modest and transient reduction of bone-formation markers with no suppression of bone-formation rate. Adverse reactions with odanacatib were close to those with placebo and scleroderma-like cutaneous lesions were not seen. Currently, a phase-3 study is underway with over 16 000 postmenopausal women to assess the antifracture efficacy of odanacatib (table 4) (NCT00529373). Another cathepsin-K inhibitor, ONO-5334 is currently being assessed in a phase-2 trial in women with postmenopausal osteoporosis (NCT 00532337).

The underlying bone biology of cathepsin K could give a clue to the distinct clinical findings with odanacatib. Because cathepsin K is a key lysosomal enzyme of the mature activated osteoclast, its inhibition suppresses osteoclast function but preserves osteoclast viability. These effects might allow osteoclast-to-osteoblast signalling that maintains bone formation while suppressing bone resorption.^{69,70} These uncoupling effects of odanacatib contrast with other antiresorptive drugs such as bisphosphonates and denosumab, which enhance osteoclast apoptosis (figure 4). Denosumab is unique in that it also inhibits osteoclastogenesis and osteoclast activation. These actions at different levels of osteoclast cell-biology could explain why bone biopsy samples from patients treated with denosumab have no osteoclasts in more than 50% of samples.⁵⁸ The importance of giant osteoclasts, of which one-third was apoptotic,⁷¹ in patients treated with bisphosphonates, is not fully understood. Whether differences in these novel, and in part hypothetical, biological concepts, will translate into meaningful clinical endpoints remains to be seen.

Saracatinib

The effect of impaired osteoclastic functions in src-deficient mice provided the rationale to explore the skeletal effects of an inhibitor of src kinase. In a phase-1 trial,⁷² saracatinib (AZD0530) was assessed in 59 healthy young men. Saracatinib dose-dependently decreased serum concentrations of CTX by 88% and urinary

Panel 3: Properties of ideal osteoporosis treatment

- Anti-fracture efficacy at various skeletal sites, including spine, non-vertebral sites, and hip
- High safety margin, both skeletal and extra-skeletal
- Mode of administration and treatment interval translate into patient's adherence
- Compatibility with drugs prescribed for other medical conditions
- Affordable cost

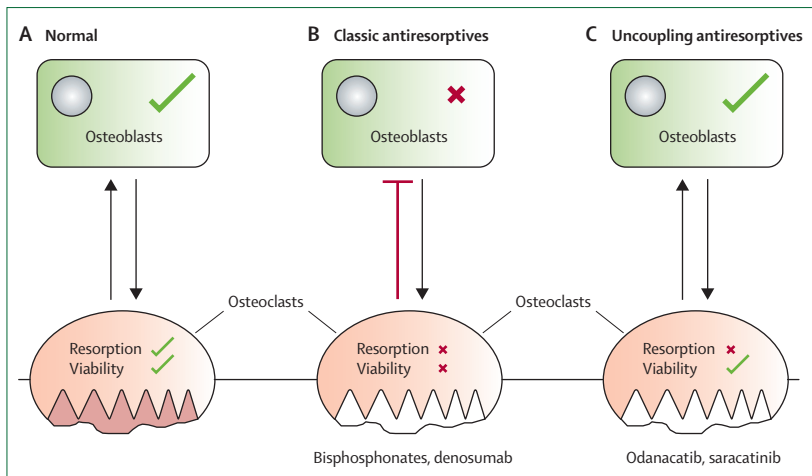


Figure 4: Potential mechanisms of antiresorptive drugs

This theoretical concept is based on cellular, preclinical, and early clinical data that need clinical validation.

(A) Physiologically, osteoclastic and osteoblastic functions are coupled with bidirectional communication. (B) Classic antiresorptive drugs act by reducing osteoclast viability. As a consequence, osteoclastic signalling and subsequently osteoblastic bone formation are suppressed. (C) Uncoupling antiresorptive drugs inhibit osteoclast activity rather than osteoclast viability, thus allowing physiological communication between osteoclasts and osteoblasts with maintained osteoblastic bone formation. OB=osteoblast. OC=osteoclast.

excretion of NTX by 67% (250 mg) after 25 days. Concentrations of bone-formation markers in the saracatinib group were similar to those in the placebo group. Although there were no significant differences between these two groups, papular rash (30% vs 6%) and loose stools (24% vs 0%) were more frequent in the men given saracatinib than in those given placebo.⁷² Saracatinib is currently being explored in phase-2 studies for osteosarcoma (NCT00752206) and bone metastases (NCT00558272), but not for osteoporosis.

Other antiresorptive therapies

On the basis of preclinical models, additional osteoclastic targets are being assessed. Eating reduces bone remodelling through release of glucagon-like peptide-2 (GLP-2), whereas nocturnal fasting enhances bone remodelling.⁷³ Treatment with GLP-2 at night for 4 months increased BMD at the hip by 1.1% from baseline, but not that of the lumbar spine, and did not suppress bone-formation markers.⁷⁴ Other strategies involve inhibition of Atp6v0d2, a subunit of v-ATPase that is needed for acidification and the voltage-gated chloride channel ClC-7.⁷⁵ The chloride-channel inhibitor NS3736 prevented bone loss in ovariectomised rats through a marked antiresorptive effect, without impeding bone-formation markers.⁷⁵ Another concept that has been assessed, but is currently no longer pursued, included antibodies against integrins that impaired the capability of osteoclasts to attach to bone and form the sealing zone.

Anabolic therapies

By contrast with antiresorptive therapies, anabolic drugs enhance bone formation instead of preventing further

bone loss, and result in a faster increase of bone mass and strength. Currently approved anabolic agents are limited to PTH either as the N-terminal (1–34) fragment, teriparatide, or the full-length PTH (1–84). PTH (1–84) has not been approved in the USA.⁵⁰

Calcilytic drugs (MK-5442)

Calcilytic drugs represent a new class of bone-forming drugs. They act as antagonists of the CaSR and mimic hypocalcaemia, thus evoking a short pulse of PTH secretion (figure 3). Calcilytics are given orally and obviate the need for injections, as opposed to PTH treatment. A major practical obstacle for these drugs has been their narrow therapeutic index. Conceptually, a high-amplitude PTH pulse followed by rapid normalisation translates into a bone-anabolic effect. Several programmes involving calcilytic drugs have been discontinued because of unfavourable pharmacokinetics⁷⁶ and lack of efficacy (NCT00471237). These compounds led to sustained PTH secretion and findings that were reminiscent of primary hyperparathyroidism, a catabolic bone disease. Currently, newer calcilytic drugs with an improved pharmacological profile are being assessed.^{77,78} The most advanced compound of this class is MK-5442, which is currently in phase-2 trials for postmenopausal osteoporosis. Results will be available in 2012 (table 4).

Inhibitors of Wnt antagonists and antibody therapies

Wnt-dependent nuclear accumulation of β -catenin (figure 3) is a major trigger of osteoblastic differentiation and bone formation.⁷⁹ The endogenous inhibitors of Wnt signalling, sclerostin and Dkk-1, present potential therapeutic targets to enhance osteoblastic bone formation and are under clinical investigation.⁸⁰

Sclerostin antibodies

Two rare skeletal diseases with a high bone mass, van Buchem's disease and sclerosteosis, have been linked to inactivating mutations in the gene coding for sclerostin.^{81,82} This finding highlighted the role of sclerostin in the homeostasis of bone mass, and provided the rationale to target sclerostin with monoclonal antibodies to enhance bone formation. In a rat model of postmenopausal osteoporosis due to ovariectomy, treatment with a sclerostin antibody increased bone mass at all skeletal sites and completely prevented bone loss associated with oestrogen deficiency.⁸³ Treatment of cynomolgus monkeys with two once-monthly injections of sclerostin-neutralising antibodies increased bone mass at the femoral neck, radius, and tibia, from 11% to 29%, and enhanced bone strength at the lumbar spine.⁸⁴ In a phase-1 study,⁸⁵ a single subcutaneous injection of sclerostin antibodies (3 mg/kg) was well tolerated and increased bone-formation markers by 60–100% at day 21. Of note, the combination of stimulated bone-formation and unchanged bone-resorption markers indicates an uncoupling effect. A phase-2 trial has been started to

compare the efficacy of sclerostin neutralisation with alendronate and teriparatide (table 4).

Dickkopf-1 antibodies (BHQ-880)

Neutralisation of Dkk-1 is still limited to preclinical trials. Blockade of Dkk-1 inhibited bone loss in a model of rheumatoid arthritis.⁸⁶ In a myeloma model, the inhibition of Dkk-1 prevented the formation of osteolytic lesions and increased bone-formation rate.^{87,88} Dkk-1 inhibition is currently being investigated in patients with refractory multiple myeloma (NCT00741377). However, the effects of neutralisation of Dkk-1 have not yet been investigated in osteoporosis. Of note, increased Wnt signalling has been associated with human malignancies such as colorectal and hepatocellular cancer.⁸⁹ More importantly, the Wnt inhibitory factor 1 (WIF), an endogenous inhibitor of Wnt signalling, was absent in 75% of osteosarcomas, leading to enhanced Wnt signalling.⁹⁰ Although patients with van Buchem's disease and sclerosteosis carry no increased risk of malignancies,^{91,92} long-term blockade of Wnt antagonists needs careful monitoring for skeletal and extraskelatal safety.

Conclusion

With multiple novel antiosteoporotic compounds in advanced clinical trials, the number of available drugs will increase considerably in the coming years. Present antiresorptive treatments are effective, but some are limited by side-effects, concurrent comorbidities, and inadequate long-term compliance. Many of the new drugs combine efficacy with convenient administration that might translate into better adherence. However, conventional antiresorptives such as aminobisphosphonates and denosumab can profoundly suppress bone resorption and formation (figure 4), which might contribute to the pathogenesis of osteonecrosis of the jaw. Some of these issues are still under debate, and long-term clinical data are needed. By contrast, odanacatib and to a certain extent saracatinib represent a distinct class of antiresorptives that inhibit osteoclast activity rather than impairing osteoclast viability. Through these distinct cellular mechanisms, paracrine signalling from osteoclasts to osteoblasts is maintained with suppressed bone resorption and concurrent normal osteoblastic bone formation, consistent with an uncoupling effect (figure 4). Whether these uncoupling compounds have an advantage over conventional antiresorptives remains to be seen. There is a great need for additional and affordable anabolic treatments in situations of severe osteoporosis, extensive bone loss, and impaired fracture healing. Calcilytic drugs and antagonist of Wnt inhibitors are promising developments.

With novel bone drugs on the brink of clinical approval, treatment of osteoporosis might become increasingly complex, especially for the general practitioner. Thus, successful integration of these novel compounds into an evidence-based concept of osteoporosis therapy requires

simple and applicable tools for clinical decision making. In some instances, such as in treatment failure, after a drug holiday, or before switching from antiresorptive to anabolic treatment, biochemical markers of bone turnover might be an adjunct to DXA to guide and monitor therapy.

With a variety of novel drugs that use the advanced knowledge of bone-cell biology, we have expanded our toolkit to facilitate the treatment of patients with osteoporosis and other skeletal diseases, thus offering more individualised treatment. Indeed, the development of these many novel compounds is an excellent example of the investment needed in basic research to identify specific pathways that can be effectively targeted to treat and possibly reverse osteoporosis.

Contributors

TDR contributed to the design, literature search, writing, and figure design. SK participated in the writing and review. LCH contributed to the design, writing, figure design, and review.

Conflicts of interest

TDR has received reimbursement of travel and accommodation expenses from Novartis. SK has received honoraria for serving on advisory boards for Bone Therapeutics and Pfizer. LCH has received honoraria and speakers fees, including reimbursement of travel and accommodation expenses, from Amgen, Daiichi Sankyo, Merck, Novartis, Nycomed, and Servier.

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