Promising developments in osteoporosis treatment

Osteoporosis is a very common disease that affects both men and women and produces an important burden. Fracture prevention is the primary treatment goal for patients with osteoporosis. There are several treatments available nowadays with anabolic, antiresorptive or dual actions. A great number of new drugs are under study. In this brief review, we highlight the knowledge regarding them so far.

KEYWORDS: activin receptor anabolic agents antiresorptive calcium-sensing receptor dkk1 odanacatib osteoporosis parathyroid hormone sclerostin treatment

The concept of osteoporosis was introduced in 1990 as "a skeletal disorder characterized by low bone mass and compromised bone strength, resulting in increased bone fragility and susceptibility to fracture" [1]. This definition comments on the intimate association between fractures and bone strength and provides a useful framework for reviewing recent developments and advances involving the diagnosis and management of individuals with compromised bone strength [2]. Osteoporosis is a very common disease that can occur in populations of all types and ages, having significant physical, psychosocial and financial consequences [3]. Fracture prevention is the primary treatment goal for patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures, including those that enhance bone mass and reduce the risk or consequences of falls. In this article we briefly review some promising new treatments for osteoporosis.

New assessment tools for fracture risks & treatment decisions

New tools have been developed in order to facilitate both the diagnosis and management of bone metabolic diseases. They are useful to estimate the long-term risk of suffering a fracture and sometimes would advise to indicate a treatment or even sometimes to discontinue them. These tools are FRAX[®], Study of Osteoporosis Fractures (SOF) and QFractureTM.

FRAX & SOF

The WHO developed a computer-generated algorithm, FRAX, which will supply clinicians with a tool to estimate absolute, time-specific fracture risk quantitatively [4–6]. This useful tool provides country- and ethnic-specific 10-year hip and major osteoporotic fracture (hip, distal forearm, shoulder, vertebral body) risks, based on information entered into the calculator, which is available for free online [101]. The information requested can be easily obtained from simple questioning; it includes age, sex, weight, height, personal and family history of fracture, current tobacco and alcohol consumption, corticosteroid usage, previous conditions associated with secondary osteoporosis, and history of rheumatoid arthritis. In the USA, bone density values at the hip are also included in the data. Threshold values for the instauration of bone-strengthening medication are established for those individuals who have a 3% or more risk of a hip fracture and/or 20% risk or more of a major osteoporotic fracture. The FRAX calculator is particularly useful for younger, healthy, postmenopausal females with osteopenia, a group of people with a relatively low 10-year fracture risk.

The American SOF Research Group has also created another assessment tool for fracture risk. The SOF model, unlike FRAX, is based only on BMD and age. However, it predicts the 10-year risk of hip and major osteoporotic fracture as well as the FRAX tool in a group of postmenopausal females, 65 years and old [7,8]. These findings highlight the importance of age as a risk factor for fragility fractures.

Both the FRAX and SOF models have demonstrated that older people with low bone density and a history of fragility fracture are at highest risk for sustaining further fragility fractures.

QFracture

A third tool, named QFracture, was also published recently. It has some similarities to FRAX, and estimates 10-year risks of fracture (major

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osteoporotic fracture and hip fracture) from a number of risk factors [9], accessible free at [102]. It has the advantage of not requiring densitometry. For a given patient, the estimated risks obtained with both tools can sometimes be similar but sometimes not. The differences between FRAX and QFracture can be seen in Box 1. The exact value of QFracture in the management of osteoporosis and the advantages or disadvantages compared with FRAX need to be studied.

The greater concerns regarding the potential adverse effects and costs of long-term use of antiresorptive agents is likely to be increasing the interest in identifying and treating those individuals who have a significantly increased absolute fracture risk. Fracture assessment tools provide critical quantitative information on fracture risk and may aid in this endeavor.

Anabolic agents

Anabolic agent activity includes not only a bone mass increase greater than the one achieved with antiresorptive agents, but also an improvement in bone quality and increase in bone strength, partly by affecting density, connectivity and geometric features among other processes involving the microstructure of the bone.

Parathyroid hormone

The changes in bone density during parathyroid hormone (PTH) treatment are measured by quantitative computed tomography, a volumetric measure of bone mass. This shows significantly greater increases than with dual X-ray absorptiometry, an areal measure of bone mass. On the other hand, the changes in bone quality cannot be detected by current clinical measures of drug response (levels of bone turnover markers and dual X-ray absorptiometry). A study by Vhale *et al.* in 2002 suggested that the use of teriparatide should be limited to 24 months due to the risk of developing osteosarcoma. This was reported to happen in a few rats receiving very high doses of PTH(1-34) [10]. However, since its release in 2002, and to date, PTH use does not appear to be associated with the development of osteosarcoma in humans and in the future it should be possible to increase the period of PTH use.

An important limitation for the long-term use of this drug is the route of administration; PTH has to be injected daily. Regardless, some promising studies have been published reporting the effectiveness of PTH administered in a nasal spray. Matsumoto et al. randomly assigned 92 osteoporotic women aged 52-84 years to receive either 250 µg (PTH250, n = 31), 500 µg (PTH500, n = 30), or 1000 µg (PTH1000, n = 31) of daily nasal hPTH(1-34)spray for 3 months [11]. In addition, all participants received supplemental calcium (300 mg) and 200 IU of vitamin D daily. Results of the study showed an increase by 2.4% of the BMD at lumbar spine in the 31 women assigned to the PTH1000 group compared with baseline measurements (p < 0.05), as well as a nonstatistically significant increase in BMD of women randomized to PTH250 and PTH500 groups. The studies based on this new route of administration may support a more important role of PTH as an upcoming treatment for osteoporosis.

Calcium-sensing receptor

The calcium-sensing receptor is located in the parathyroid gland and the kidney. It is a G-protein-coupled, seven-pass transmembrane molecule whose main function is to coordinate

Box 1. What is the difference between QFracture[™] and FRAX[®]?

- Practure is suitable for use in patients aged 30–85 years whereas FRAX is suitable for patients aged 40–90 years
- FRAX includes humerus fractures in the fracture score as well as hip, vertebral or distal radius fracture
- QFracture was developed and validated on an extremely large and representative primary care population. It has been specifically designed for use in primary care. FRAX was developed and validated on multiple clinical trial cohorts assembled for different studies at different times
- QFracture includes a more detailed assessment of smoking and alcohol intake than FRAX. This is because the evidence suggests that the effects of smoking and alcohol are dose dependent
- FRAX has been adapted for international use whereas the current version of QFracture is designed for use in the UK
- QFracture has additional factors which are not included in FRAX and therefore may provide a more individualized assessment of risk. The factors included are:
- History of falls
- Type 2 diabetes
- Cardiovascular disease
- Tricyclic antidepressants
- Hormone replacement therapy
- Menopausal symptoms (vaginal dryness, hot sweats)

Data taken from [9].

calcium homeostasis by regulating the release of PTH [12]. Therefore, small-molecule allosteric modulators can modify the PTH secretion. Thus, positive allosteric modulators or calciumsensing receptor agonists, named calcimimetics, such as cinacalcet, decrease PTH secretion in patients with renal disease and hyperparathyroidism; while negative allosteric modulators or calcium-sensing receptor antagonists, named calcilytics, such as ronacaleret, can inhibit the receptor, releasing a PTH pulse following each dose, reason why they are being developed for the treatment of osteoporosis. Opposite to PTH, that needs to be injected daily, these agents can be administered orally [13].

Calcilytics must stimulate the release of sufficient PTH; have a short half-life and transient activation of the receptor, as sustained activation would result in prolonged PTH secretion and a catabolic state (hyperparathyroidism); and the molecule should not exhaust the parathyroid gland and not result in hyperplasia to be useful as anabolic agents.

A study with the calcilytic ronacaleret has shown a great PTH response increasing both cortical and trabecular bone formation in rats, as well as notable increases similar to those observed with teriparatide in propeptide of type I procollagen, osteocalcin and bone-specific alkaline phosphatase, all markers of osteoblast function. Ronacaleret was also proven to have a mean terminal half-life of 4-5 h, and the postdose PTH peak increased in a dose- and concentration-dependent manner (by 300-900%). Adverse effects were mild to moderate and consisted chiefly of headaches and constipation or diarrhea. Its safety, pharmacokinetics and pharmacodynamics were assessed in a randomized placebo-controlled trial where 65 postmenopausal women with a mean age of 55 years were randomized to receive different doses (75 mg, 175 mg and 475 mg) twice at an interval of 28 days. The 475 mg group showed a 63% increase in osteocalcin levels, 79% for P1NP, and 35% for bone specific alkaline phosphatase (BSAP; p < 0.05 vs placebo). No statistically significant changes were observed in serum levels of C-terminal telopeptide (CTx; a resorption marker). Based on this, it can be assumed that ronacaleret will have an important role in the treatment of osteoporosis. However, a Phase II study in postmenopausal women with osteoporosis was discontinued based on lack of efficacy. Either way, these molecules represent a potential oral anabolic agent and further trials are underway [14].

Modulating the Wnt signaling pathway

Regulation of embryogenetic bone remodeling is one of the many actions in which Wnt proteins, a large family of extracellular cysteine-rich glycoproteins, are involved [10].

Wnt proteins activate an intracellular pathway that results in accumulation of B-catenin. When Wnt is not present, glycogen synthase kinase 3 phosphorylates B-catenin, which is then degraded via the ubiquitin/proteasome pathway (FIGURE 1). In the presence of Wnt, the protein complex is disrupted and phosphorylation does not occur, B-catenin accumulates, translocates to the cell nucleus, and binds to transcription factors that affect gene transcription, which are important in bone formation (FIGURE 2) [15–17].

Antibodies to sclerostin

Sclerosteosis is an autosomal recessive bone dysplasia characterized by hyperostosis and increased bone density more notable at the skull and long-bone diaphyses, caused by an inactivating mutation in the SOST gene. Sclerostin is the protein product of this gene and is expressed in various tissues but is found mainly on osteocytes. Sclerostin inhibits the Wnt signaling pathway by inactivating LRP5. Thus, sclerostin is a physiological inhibitor of bone formation [18]. Some studies have shown that overexpression of human sclerostin on transgenic mice leads to low bone mass and an increased susceptibility to fractures [19], while other studies report that mice lacking sclerostin (Sost^{-/-}) exhibit a diffuse increase in bone density [20].

Sclerostin deficiency has been proven to be the cause of sclerosteosis and van Buchem disease. This finding, along with the restricted expression pattern of sclerostin and the particular 'good quality' bony phenotype found in patients with sclerosteosis and van Buchem disease provide the basis for the design of a possible forthcoming treatment for osteoporosis based on its capability to stimulate bone formation [14]. The way to achieve this is by developing antibodies capable of inhibiting the biological activity of sclerostin, mimicking its absence in sclerosteosis. Such antibodies have already been shown to increase BMD, bone volume and bone strength in ovariectomized rats [21] and primates [22], and to reverse bone loss in a model of colitis [23].

A blinded, placebo-controlled, dose-escalating, single-dose study was performed, randomizing 48 healthy postmenopausal women to receive either a single dose of antibody (0.1–10 mg/kg; in a 3:1 ratio) or placebo. Results showed dose-dependent

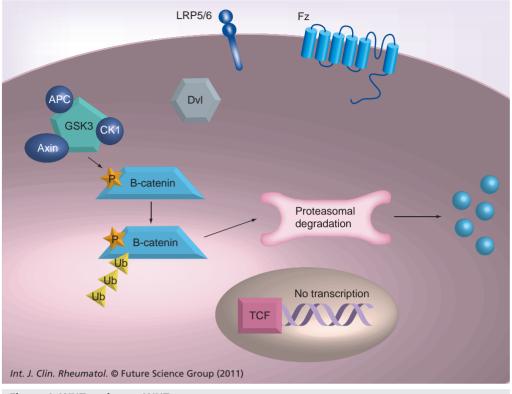


Figure 1. WNT pathway: WNT not present.

marked increase (mean increase, 60-100% with 3 mg/kg 21 days postdose) in bone formation markers (osteocalcin, P1NP and BSAP), and BMD in the antisclerostin group, statistically significant compared with the placebo; as well as a trend toward a decrease in the resorption marker serum CTx. The antibody was well tolerated [24]. P1NP serum levels peaked 14-25 days postdose and then progressively returned to baseline after 2 months. On the other hand, serum CTx, the bone-resorption marker, decreased to a minimum approximately 14 days after the antibody injection and returned to baseline values after approximately 2 months. The finding of consistently higher BMD values in carriers of sclerosteosis with no skeletal complications [25] suggests that sclerostin inhibition can be titrated and can lead to the desired outcome without any side effects, but safety margins are yet to be determined. The absence of extraskeletal complications is another important advantage to take into account in the future use of sclerostin antagonists or inhibitors to treat osteoporosis. However, there have been concerns that stimulation of bone formation by increasing Wnt signaling may lead to unwanted skeletal effects [26,27].

The Wnt inhibitor factor 1, for example, has been identified as a tumor-suppressor gene in human osteosarcoma, suggesting that the susceptibility to osteosarcoma may be increased in patients receiving novel anabolic treatments targeting Wnt [28], but this is another matter that needs further investigation.

Anti-Dkk1 antibody

Dkk1, a natural antagonist of the Wnt-pathway, inhibits interactions between the coreceptor LRP5/6 and the Frizzled Wnt-pathway receptor involved in bone formation [29]. In mice, bone mass correlates inversely with the Dkk1 expression level [30]. Dkk1 is expressed in adult bone, and inhibition of the binding of LRP to Dkk1 may stimulate bone formation.

The development and the *in vitro* and *in vivo* characterization of neutralizing monoclonal antibodies against Dkk1 in mice have been described [31]. In vitro, anti-Dkk1 antibodies block Dkk1 function, so that Dkk1 no longer inhibits the Wnt-pathway, and they also inhibit bone formation. In vivo, anti-Dkk1 antibodies have a long half-life of 17 days in mice. The partial or complete resolution of osteopenia at the femur or spine resulting from ovariectomy can be managed by administrating anti-Dkk1 antibodies once or twice a week for 2 months; this will significantly increase serum P1NP and induce new bone formation both on the endocortical surfaces and within the trabecular bone. These outcomes prove the possibility of modulating the Wnt-pathway by administering

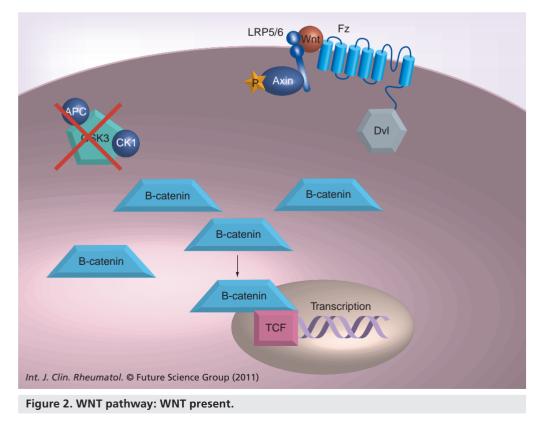
neutralizing anti-Dkk1 antibodies to animals and demonstrate the efficacy of anti-Dkk1 therapy in an animal model of bone loss induced by estrogen deprivation. As a result, anti-Dkk1 therapy may hold promise for the treatment of bone diseases characterized by low BMD values, such as osteoporosis.

Soluble activin receptor

A key signaling component in bone formation is bone morphogenic protein (BMP), a member of the TGF B superfamily [32]. Activin receptor type A (ACVR1) or activin receptor-like kinase 2 is one of the BMP receptors. The BMPs constitute a family of growth factors that play a crucial role in bone formation. Mutations affecting the ACVR1 gene may cause fibrodysplasia ossificans progressiva, a rare dominant autosomal disease whose features include skeletal birth defects and ectopic bone formation within muscles. These mutations lead to the production of an active receptor that activates intracellular BMP signaling [33]. The activin antagonist RAP-011 was developed by fusing the extracellular domain of the activin receptor type IIA to the Fc fragment of murine immunoglobulin. RAP-011 increases bone formation in both normal mice and ovariectomized mice with established bone loss, as well as in vivo BMD values, it also improves bone strength and architecture, and produces bone anabolism [34].

ACE-011 is a fusion protein that binds activin, composed of the extracellular domain of the human activin receptor type IIA and of the Fc fragment of human IgG1. The effects of a single ACE-011 injection (0.01-3 mg/kg intravenously or 0.03-0.1 mg/kg subcutaneously) were analyzed in a Phase I randomized, double-blind, placebo-controlled trial in 48 postmenopausal women [35]. The follow-up was set at 120 days. At that time, headaches, nausea and vomiting, and injection-site reaction were found out to be the main adverse events, without any record of serious unwanted effects. Blood levels were linearly related to the dose, and the half-life was 25-32 days. ACE-011 injection was rapidly followed by a sustained dose-dependent increase in BSAP levels and decrease in CTx and TRAP-5b levels. These changes persisted for at least 28 days with the highest doses studied. A dose-dependent decrease in serum FSH levels reflecting activin inhibition was also observed.

Bone mass effects and pharmacokinetics of ACE-011 were assessed in cynomolgus monkeys (n = 5/group), which received 10 mg/kg of ACE-011 subcutaneously, or the vehicle twice a week over 3 months [36]. After this period, BMD was markedly higher in the ACE-011 group than in the vehicle group (+13% at the spine, p < 0.01; +15% at the femur, p = 0.05). Improvement of the structural parameters was



observed alongside increased trabecular bone number (+11%, p = 0.04) and volume (bone volume/tissue volume, +16%, p < 0.01) on microcomputed tomography. In humans, a single dose of the fusion protein (ACE-011), was administered to 48 healthy postmenopausal women, resulting in an increase in BSAP and a decrease in C-telopeptides [37]. These results suggest that ACE-011 stimulates bone formation and diminishes bone resorption, and could also be a new anabolic treatment for osteoporosis. However, there are very few studies on humans, therefore further investigation is pertinent.

New resorption inhibitors Odanacatib

Ondanacatib inhibits cathepsin K, causing inactivation of its preoteolytic activity in osteoclasts. The presence of the 4-fluoroleucine side chain at the P2 position interacting within the S2 pocket is what gives ondanactib its potency and selectivity [38]. This is responsible for the lack of accumulation of undesirable collagen in cutaneous fibroblasts [39].

A Phase I study has been performed in order to determine the dose and a Phase II study has been carried out to assess ondanacatib's safety and efficacy. This study proved that ondanacatib's long half-life would allow a weekly administration, showing no significant differences with those randomized to daily administration when assessing suppression of bone resorption markers. No adverse effects were observed [40]. Based on the data from the Phase I trial, the Phase II trial used different doses of odanacatib on a weekly basis. Best effects were achieved with a dose of 50 mg/week [41].

The Phase II study was extended up to 36 months. At this time, increases in BMD achieved were similar to those of most powerful antiresorptive agents (zoledronate and denosumab), but with differences in the behavior of bone remodeling markers. A smaller reduction in markers of resorption was observed compared with that obtained with other antiresorptives but, on the other hand, the reduction in levels of formation markers was much smaller [42–45]. There are no data on fractures, but there is a study being carried out at present, with results expected in 2012.

Glucagon-like peptide 2

Glucagon-like peptide (GLP)-2 is an intestinal polypeptide hormone released in response to food intake. Bone remodeling occurs according to a circadian rhythm [46] that is affected by rates of food intake and increases overnight with nocturnal fasting. Bone resorption activity peaks overnight; therefore, treatment with GLP-2 at bedtime will achieve a substantial reduction in the bone resorption. However, GLP-2 does not appear to reduce bone formation, as evidenced by stable osteocalcin levels during treatment [47]. A study performed in postmenopausal women who were assigned to receive subcutaneous GLP-2 therapy for 14 days showed significantly diminished bone resorption without affecting bone formation or osteocalcin levels [46]. Similarly, a Phase II placebo-controlled trial was performed in 160 postmenopausal women with osteopenia who were given a daily GLP-2 subcutaneous injection (doses were 0.4 mg, 1.6 mg or 3.2 mg). After 120 days a dose-dependent increase in hip bone density and a reduction in the nocturnal rise in CTx concentrations, a marker of bone resorption, were observed with no effect on osteocalcin, a marker of bone formation. GLP-2 effects were statistically significant, with the highest dose (3.2 mg/day) at the total hip and trochanter. These results suggest that GLP-2 may dissociate bone resorption from bone formation [48]. If this pattern could be sustained, GLP-2 would have a great advantage over other available antiresorptive agents that decrease bone formation and hold promise in the treatment of osteoporosis.

Future perspective

Treatment of osteoporosis has changed substantially in recent years. Only 15 years ago, we had calcitonin, estrogen, etidronate and alendronate. Today, the therapeutic arsenal is huge and varied and we have a deeper understanding of the side effects that occur as a consequence of prolonged use of some drugs such as bisphosphonates.

New drugs are emerging for the treatment of osteoporosis, characterized by acting on very specific bone cell physiology, and sometimes it is almost a true therapy with monoclonal antibodies that regulates bone cell pathophysiology. Perhaps the most important aspect that remains is to check there are no major side effects in the long term.

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Executive summary

Osteoporosis: definition & epidemiology

- Osteoporosis is a very common disease, which affects both men and women and produces an important burden.
- A total of 1.7 million hip fractures occurred worldwide during 1990 and this is projected to increase to 6.3 million per year by 2050.

Main clinical complication of osteoporosis

- Fracture is the main, and only, clinical complication of osteoporosis.
- Fractures most commonly related to osteoporosis are vertebral, hip, foream (Colles') and humerus fracture. Nevertheless, any fracture may occur.

Main objective in the treatment of osteoporosis

- Fracture prevention is the primary treatment goal for patients with osteoporosis.
- Nowadays, most drugs used in the treatment of osteoporosis reduce the risk of suffering new fractures by approximately 50–60%. No one treatment can remove all risk.

New assessment tools for fracture risks & treatment decisions

- FRAX[®] is a tool that permits estimation of the risk of suffering a fragility fracture in the next 10 years.
- FRAX is supported by the WHO and can be accessed on the internet.
- QFracture[™] is another tool that permits estimation of the risk of suffering a fragility fracture in the next 10 years.
- QFracture and FRAX estimate the risk of future fractures using similar risk factors. QFracture is more complete but FRAX is supported by WHO.

Drugs currently used in the treatment of osteoporosis

- A great number of new drugs are under study for use in the treatment of osteoporosis.
- Anabolic drugs create new bone by stimulating the action of osteoblasts.
- New anabolic drugs include new parathyroid hormone formulations, calcium sensing receptor modulators (ronacaleret), drugs that act by modulating the Wnt signaling pathway (antibodies to sclerostin, anti-Dkk1 antibodies) and soluble activin receptor mdulators (ACE-011).
- New antiresorptive drugs are: ondanacatib, inhibiting cathepsin K and glucagon-like peptide 2.

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