Acta Biomed 2010; 81; Suppl 1: 55-65

Review

Therapeutic options in osteoporosis

Ligia J. Dominguez, Rosalinda Scalisi, Mario Barbagallo
Geriatric Unit, Department of Clinical Medicine and Emergent Pathologies, University of Palermo, Italy

Abstract. Osteoporosis is a major and global public health concern. This disorder is characterized by a compromised bone strength and increased susceptibility to fractures, with important health and socioeconomic consequences. Age remains a cardinal, independent determinant of fracture risk; hence, the prevalence of osteoporotic fractures is expected to rise as the proportion of older populations increases worldwide. The prevention of osteoporosis should begin early and continue all the way through life with measures that improve or maintain bone health including regular physical activity and a balanced diet, considering not only an adequate intake of calcium but also of other minerals, proteins, and food rich in antioxidants. Smoking and alcohol abuse should be avoided. In older persons, who are particularly at risk of fragility fractures, the prevention of falls and the maintenance of an adequate vitamin D status are essential. Assessment of fracture risk followed by proved effective nonpharmacological and pharmacological management is still low, even in patients who have sustained a fragility fracture. Nonpharmacologic strategies should always be implemented, but many patients also need pharmacologic intervention to achieve adequate fracture protection. It is clear today that although low bone mineral density (BMD) is an important determinant of bone fragility, it is not the only one, hence, drugs used in the treatment of osteoporosis must not only show to promote changes in BMD, but to reduce the incidence of fractures. Safety issues should be always considered in an individual basis. This article reviews the available nonpharmacologic and pharmacologic interventions -proved to be effective- that may be implemented to reduce the risk of osteoporotic fractures. (www.actabiomedica.it)

Key words: Osteoporosis, fractures, falls, vitamin D, malnutrition, physical activity, bisphosphonates, teriparatide, strontium ranelate, parathyroid hormone

Osteoporotic fractures are one of the major public health concerns worldwide, expected to increase in an exponential manner in the near future (1). This common disorder is an important cause of morbidity and mortality that places a substantial economic and health burden on the society. It is well known that lifetime risk of fractures is increased in women during the postmenopausal period and vertebral fractures account for most of the fractures observed in menopause (2). Nevertheless, an increasing amount of research has been dedicated in recent years to the occurrence of osteoporosis in men, which also appears to be an important health problem and as relevant as it is for women (3). Even if osteoporosis can affect any district of the skeleton, fractures occur most commonly in the vertebrae and proximal femur and may result in chronic pain, disability, and death (4). After a hip fracture, approximately 20% of persons die within one year, 30% of persons have permanent disability, 40% cannot walk independently, and 80% have lost at least one IADL. In Italy, the direct costs of hospitalization for hip fractures registered in 2002 were about 400 million euros, with an increase of 15% as compared to 1999 costs. When considering also rehabilitation costs, social aid and indirect costs, the costs estimates exceeded one billion euros (5). Several certain risk factors for osteoporosis have been identified such as age, reduced physical activity, a prior fragility fracture, a family his-

tory of an osteoporotic fracture, use of corticosteroids, and alcohol abuse (6). Among these factors, age remains a cardinal determinant with independent effects on fracture risk. As the proportion of the elderly population increases worldwide, the prevalence of osteoporosis and related fractures is expected to continue rising.

Although low bone mineral density (BMD) is commonly used to diagnose osteoporosis, it does not identify all patients at risk. In a study that examined the number of women with fractures within the year following BMD measurement, 82% of postmenopausal women with fractures had T-scores better than -2.5 SD (7). Hence, the assessment of fracture risk needs to take into account a number of clinical risk factors that provide information on fracture risk beyond that given by BMD. The WHO-FRAX algorithms integrates the influence of several well validated risk factors for fractures, with or without the use of BMD, over the next 10 years, allowing to offer treatment to persons with a fracture probability greater than an intervention threshold (8).

This article reviews the available nonpharmacologic and pharmacologic interventions that may be implemented to reduce the risk of osteoporotic fractures.

Non Pharmacologic Strategies

In general, nonpharmacologic interventions slow or stop bone loss, maintain bone and muscle strength, increase bone strength, or reduce/remove factors that may result in fractures (9) (Table 1). Indeed, nonpharmacologic measures are recommended for the population as a whole, not just for patients with osteoporosis. Even if several effective pharmacological options are available, and many others with relevant mechanisms of action are under development, it should not be forgotten that nonpharmacological strategies can achieve results comparable to those of drugs. This include a reduction of fracture incidence by ~33% with correction of visual acuity impairments, by ~40% with reduction in sedatives usage, by ~30% with daily walking, and by ~40% with smoking cessation (10).

Table 1. Nonpharmacologic strategies

- Lifestyle modifications
  - A balanced diet
  - Moderate, regular physical activity
  - Avoid prolonged immobilization
  - Avoid unnecessary use of sedatives or hypnotics (favor falls)
  - Avoid unnecessary use of corticosteroids
  - Avoid heavy lifting
  - Avoid alcohol abuse
  - Avoid smoking
- Fall prevention (see Table 2)
- Calcium and vitamin D
- Other nutritional factors: adequate intake of protein, magnesium, phosphate, vitamin K, vitamin C, vitamin B_{12}, vitamin B_6, zinc, selenium; avoiding excess of salt and alcohol
- Hip protectors
- For patients with severe osteoporosis:a physical and psychological rehabilitation program, and the use of assistive devices (i.e. cane and walker)

Physical Exercise

Exercise and muscle strengthening connote a myriad of health benefits. Even if weight-bearing exercise may result in only modest increases in bone density, the improvements in agility, strength, and balance that accompany regular weight-bearing exercise and muscle strengthening may significantly reduce the risk of falls and subsequent fracture, independently of an increase in bone density. High-impact exercises (e.g., running, gymnastics, or high-impact aerobics) appear to provide the most osteogenic stimulation (9). Exercise can improve balance, gait, coordination, proprioception, muscle strength, and reaction time in elderly persons (11). A study showed that a program of regular exercise (30 min 3 times a week) prevented or reversed almost 1% of bone loss per year at vertebral and femoral sites in postmenopausal women (12). Although RCTs with physical exercise as an intervention and fractures as endpoint are lacking, a recent extensive medline review confirmed the compelling effects of physical activity on the reduction of risk factors for falls (13).

Fall prevention

Because falls play a role in ~90% of fractures (9), fall prevention is a major issue in patients with osteo-

Table 2. Risk factors for falls in the elderly

- Advanced age
- Housebound status
- Muscle strength reduction
- Gait and balance disturbances
- Postural hypotension
- Use of sedatives or hypnotics
- Use of more than 4 drugs
- Reduced vision
- Decreased hearing
- Vitamin D deficit
- Previous falls
- Cognitive impairment
- Foot problems and shoe wear (low-heeled and soft-soled)
- Use of cane or walker
- Acute illness
- Chronic diseases (especially neuromuscular disorders)
- Neurological modifications, including age-related changes (i.e. postural instability, slowed reaction time; syncope, drop attacks, epilepsy)
- Architectonic barriers
- Risky behaviors (i.e. alcohol abuse)

porosis (Table 2). Most of these falls are associated with identifiable risk factors (i.e. unstable gait, weakness, confusion and certain drugs) and the attention to these risk factors can significantly reduce the rates of falling (14). Falls are a relevant economic burden to society (14, 15), hence, fall-prevention programs aiming at reducing fall-related fractures may contribute substantially to abate fall-related costs. Fall-prevention strategies include checking and correcting vision and hearing acuity, evaluating neurological problems, reviewing medications for adverse effects that may affect balance or stability (i.e. benzodiazepines, neuroleptics, antidepressants, excessive antihypertensive drugs), promoting exercise, and eliminating safety hazards at home (installing grab bars/handrails, providing adequate lighting, and eliminating obstructions) (14).

Smoking

Smoking results in a more rapid rate of bone loss by interfering with calcium absorption and lowering estrogen levels (16). Decreased bone density is one of the many detrimental effects of smoking tobacco; hence, all patients should be encouraged to stop smoking. Heavy smoking for many years in life may lead to chronic obstructive pulmonary disease or asthma, which is associated with lower BMD at the spine and hip and increased risk of vertebral and nonvertebral fractures independent of age, clinic site, BMI, and smoking.

Alcohol abuse

Heavy alcohol consumption (defined as more than seven drinks per week) has been associated with an increased risk of falls and a decrease in BMD, hence, patients with osteoporosis should be counseled about excessive drinking (6). Alcohol's direct effect on bone cells together with alcoholism-related lifestyle factors, such as malnutrition, lack of exercise, hormonal changes, falls, and liver cirrhosis may have additive effects as causes of fragility fractures (17). Patients with chronic alcohol abuse present a clinical picture of malnourishment because of reduced usual intake of essential nutrients and because alcohol precludes an appropriate digestion and absorption of the different essential elements, vitamins, and minerals. Deficit of protein, calories, vitamin D, A, C, B_{12}, K, calcium, magnesium, selenium, phosphate, and/or zinc may be observed in the chronic alcoholic patient (18).

Nutritional factors

A well-balanced diet is important for promoting general health, including good bone health. Maintenance of optimal bone mass requires adequate consumption of vitamins (i.e. D, K, C, B_{12}, B_6), minerals (calcium, magnesium, zinc), and protein (9, 19-22). Dawson-Hughes and Harris also found an association between protein intake and calcium/vitamin D supplementation with increases in BMD (23), that suggests possible interactions among different nutrients. High fruit and vegetable intake appears to be protective in men. High candy consumption was associated with low BMD in both men and women (24). In children, the consumption of sweetened drinks may displace milk consumption, resulting in calcium deficiency with an expected higher risk of osteoporosis and fractures (25). Excess sodium intake, reflected by urinary Na/Cr ratio, has been linked to an inverse relationship with BMD (26), and it may be responsible for an inadequate bone calcium balance (27).

Calcium and Vitamin D

Adequate intake of calcium is essential for maintenance of bone health. For premenopausal women <50 years of age, the generally recommended daily intake of calcium is 1000 mg, and for postmenopausal women and elders the recommendation is of 1500 mg daily (9). Although dietary sources (i.e. dairy products and vegetables) should be the primary source of calcium, intake can be augmented through the use of calcium supplements or calcium-fortified food when necessary. Calcium supplements are best absorbed when taken in divided doses, with single doses ≤1000 mg (9).

An adequate intake or supplementation of calcium and vitamin D is crucial in frail and institutionalized elders at highest risk of fractures due to secondary hyperparathyroidism and increased propensity to falls. One of the first controlled trials with positive results was conducted in a large population of elderly women in nursing homes and demonstrated that the daily use of a supplement (1.2 g calcium and 800 IU vitamin D3) reduced hip fractures by 23%, and decreased PTH by 28% (28). However, a meta-analysis (29) and some RCT (30-32) have shown no significant difference between calcium supplementation alone and placebo in the prevention of vertebral, nonvertebral, and hip fractures in postmenopausal women. These results may have been influenced by lack of consideration of adherence to the therapy. Indeed a study including an adherence analysis found a reduction in fractures (30), and a recent meta-analysis showed a reduction in relative risk for fractures with calcium treatment alone (33). Even if studies on the effects of calcium supplementation on the prevention of bone loss and fractures have shown inconsistent results, it is worth mentioning that each and every one of the pharmacological trials for osteoporosis included calcium and vitamin D as part of the treatment.

Vitamin D plays a major role in calcium absorption and bone health. This vitamin, also considered a hormone, is the cofactor that facilitates calcium intestinal absorption and renal reabsorption. Vitamin D deficiency is very frequent to the point of considering it a pandemic (34) that causes osteomalacia and osteoporosis in adults. Few food sources contain naturally occurring vitamin D. Sources of ergocalciferol include eggs, fish oil, vitamin D-fortified milk, fortified cereals, butter, salmon, herring, and liver. The recommended daily intake of vitamin D is 400 to 600 IU for all adults >50 years of age. In those at risk of vitamin D deficiency due to inadequate exposure to sunlight, doses of 700 to 800 IU/d are recommended. In a recent report, doses of 800 to 1000 IU/d of vitamin D were recommended by an expert panel to lower fracture risk in the elderly (35). An adequate vitamin D status is not only important to maintain bone health but its supplementation appears to reduce the risk of falls among ambulatory and institutionalized older individuals by over 20% (36). Vitamin D supplementation is low even in patients who underwent a hip fracture. In a study of 222 consecutive hip fracture patients over a 12 month period, severe vitamin D deficiency <30 nmol/l was present in 60%; 80% were <50 nmol/l, and less than 4% reached desirable levels of at least 75 nmol/l. Only 10% of hip fracture patients had any vitamin D supplementation on admission to acute care (37).

Some meta-analyses reported no effect on fracture risk for different preparations of vitamin D (38, 39). Conversely, other meta-analyses showed a significant reduction on nonvertebral and hip fractures with vitamin D supplementation (32, 33). These differences may be due to different vitamin D status and calcium intake at baseline, different doses and poor to adequate compliance. In fact, an initial report from the Women's Health Initiative showed no evidence of fracture risk reduction with calcium and vitamin D supplementation for 7 years (40) but a post-hoc analysis showed that those complying with treatment had a 29% reduction in hip fractures. A recent meta-analysis of 12 RCTs for nonvertebral fractures (n=42 279) and 8 RCTs for hip fractures (n=40 886), considering adherence, showed that nonvertebral fracture prevention with vitamin D is dose-dependent with a higher dose reducing fractures by at least 20% for >65 years old persons (41).

Hip protectors

Anatomically designed external hip protector have been used in frail elders and in some studies have proved to reduce the risk of fractures (42). They seem

particularly useful in long-term facilities even if in this setting the compliance and protection are not definitely proven (43).

Pharmacologic strategies

The ideal profile of any drug used in the treatment of osteoporosis should not only take into account the effects on BMD but the effects on the reduction of fracture incidence. Hence, it is recommended to choose agents with evidence-based efficacy on this outcome. Furthermore, some patients at highest risk of osteoporotic fractures (i.e. based on risk algorithms such as FRAX index) may have the indication of pharmacological therapy in addition to non-pharmacological strategies even in the presence of a normal BMD. Available effective pharmacologic options with proved efficacy include: the bisphosphonates, estrogen therapy, raloxifene, the anabolic agents teriparatide and 1-84 parathyroid hormone, and strontium ranelate (Table 3). Overall these widely available therapies can reduce vertebral, hip and other fractures by 30% to 65% as will be discussed below.

Bisphosphonates

Bisphosphonates are stable analogs of inorganic pyrophosphate with a high affinity for hydroxyapatite crystals that bind selectively to mineralized surfaces of bone. These agents selectively disrupt osteoclast activity by blocking critical steps in cholesterol synthesis resulting in slower bone turnover, with concomitant benefits for trabecular integrity and connectivity (44). It has been suggested that bisphosphonates may also inhibit apoptosis of osteoblasts and osteocytes (45). The reduction in activation frequency and bone remodeling activity induce a prolonged secondary mineralization phase, leading to increases in BMD at the tissue level (46). Initially, treatment is associated with partial refilling of the remodeling space, with a moderate increase in bone matrix volume, which undergoes primary mineralization, producing a rapid increase in BMD. Subsequently, induction of a progressive increase in the mean degree of bone mineralization leads to a prolongation of the secondary mineralization phase.

There is ample evidence showing that available bisphosphonates prevent vertebral fractures and nonvertebral fractures. The Fracture Intervention Trial (FIT) demonstrated that in postmenopausal women with low BMD and a previous vertebral fracture, 3 years of daily alendronate therapy (5-10 mg/d) reduced vertebral fracture risk by 47% compared with placebo. In women with low BMD without previous fractures, 4 years of alendronate therapy resulted in a 44% reduction in vertebral fractures (47). After 3 years of daily administration of ibandronate 2.5 mg or placebo to postmenopausal women with low BMD and a history of vertebral fractures, ibandronate therapy was associated with a 62% reduction in the risk of vertebral fractures (48). Although risedronate (49, 50) and alendronate therapy are not only associated to a reduced risk of vertebral fractures but also to a significant reductions in nonvertebral fractures (including hip), therapy with ibandronate has not shown to reduce nonvertebral fractures (including hip) (48). Two large randomized trials showed that zoledronic acid prevents vertebral and nonvertebral fractures in high-risk populations and reduces the risk for hip fracture (51, 52). Interestingly, zoledronate therapy has demonstrated a reduced mortality rate after hip fracture (52).

Increase of bone structure units with a maximum degree of secondary mineralization with bisphospho-

Table 3. Pharmacologic strategies with evidence-based efficacy in fracture incidence reduction

*Antiresorptive agents**
- Estrogens
- Bisphosphonates
  - Alendronate (p.o.)
  - Risedronate (p.o.)
  - Ibandronate (p.o. and i.v.)
  - Zoledronate (i.v.)
- Raloxifen

*Anabolic agents**
- Teriparatide (s.c.)
- PTH 1-84 (s.c.)

*Dual Action Bone Agent**
- Strontium Ranelate

*Pharmacologic trials for all these agents included the association with calcium and vitamin D

nates therapy may contribute to the observed reduction of fracture incidence. On the other hand, a study reported marked inhibition of cancellous bone formation in a group of nine patients who suffered spontaneous nonspinal fractures while on alendronate therapy for 3-8 years, six of whom experienced a delay or absence in fracture healing for 3 months to 2 years (53). The osteoclastic surface was found to be low to low-normal in eight patients while four patients exhibited decreased eroded surface. Furthermore, matrix synthesis was found to be markedly diminished. Based on these observations, the authors suggested that long-term alendronate therapy may cause severe suppression of bone turnover, leading to an increased susceptibility to, and delayed healing of, nonvertebral fractures. This report has given rise to considerable debate and discussion because the histomorphometric abnormalities seen in these patients have all been reported in patients with untreated osteoporosis. It is well known that bone turnover is reduced by all antiresorptive therapies and that this effect is prolonged with bisphosphonate therapy because of the long half-life of these drugs inside the skeleton. The question of "frozen bone" has been raised often but, in all published reports of the fate of the skeleton after discontinuation of bisphosphonates, no evidence of irreversible suppression of bone remodeling has been noted (44).

The most common adverse effects associated with bisphosphonates are esophageal and gastric irritation, which may result in dysphagia, esophagitis, and esophageal and gastric ulceration. All bisphosphonates, with the exception of zoledronate, have reported gastrointestinal side effects (54). Another side effect associated with bisphosphonate therapy, even if infrequent, is osteonecrosis of the jaw, which appears to be a class-related event. It has been reported in individuals with metastatic cancer under high intravenous doses of bisphosphonates and in a small subset of individuals who have been treated with bisphosphonate therapy for osteoporosis and Paget's disease of bone (55). Osteonecrosis has been proposed to be the result of the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling due to physiologic stress, iatrogenic trauma, or tooth infection (56), although further research is needed to clearly elucidate the pathogenesis of this process. In non-oncologic patients taking oral bisphosphonates this condition is rare but the risk is uncertain and deserves careful consideration. Nonetheless, even in this circumstance, the confirmed clinical benefits of bisphophonates therapy seem to outweigh potential risks.

Estrogen

Given the relevant role of estrogen in bone metabolism, hormone replacement therapy (HRT) has been considered as an option to prevent and treat osteoporosis. There is good-quality evidence showing that estrogen reduces the incidence of vertebral, nonvertebral and hip fractures (57). However estrogen long-term use effects on cancer, coronary heart disease, stroke, and blood clots in postmenopausal women has generated extensive debate. Since it has been shown that the benefit-risk ratio for HRT decreases with aging and that HRT seems to increase the incidence of dementia when initiated in women 65 years and older (58), current guidelines recommend HRT use close to menopause, when indicated, for the shortest time possible and at the lowest dose.

Data from the National Osteoporosis Risk Assessment Study and the Million Women Study indicate that therapy discontinuation results in accelerated bone loss and may lead to increased risk of fractures (59). Data on the effects of HRT on bone architecture in postmenopausal women are limited. A prospective RCT showed that after 2 years, treatment of postmenopausal women with cyclic HRT reduced osteoclastic hyperactivity but neither induced a significant difference in marrow star volume nor exerted an anabolic effect (60). A more recent subsequent analysis of bone samples from several patients, however, associated HRT treatment with increased mineral crystallinity and collagen crosslinks ratio, suggesting that bone was more mature, as might be expected from suppressed osteoclastic activity (61).

Selective estrogen receptor modulators (SERMs)

These compounds have a high affinity for estrogen receptors exerting tissue-specific agonistic or an-

tagonistic estrogen effects (62). This pharmacologic profile allows dissociation of estrogen's unfavorable stimulatory effects on breast and endometrium from the beneficial effects of estrogen on bone and lipid metabolism. Currently, the only SERM approved by the FDA and EMEA for prevention and treatment of osteoporosis is raloxifene.

There is evidence showing that raloxifene inhibit bone resorption and considerably reduce the risk of new and recurrent vertebral fractures in osteoporotic women, but it does not have any effect on hip fractures (63, 64). Raloxifene has been associated with an increased incidence of vasomotor symptoms and venous thromboembolic events (65). This SERM does not appear to cause osteomalacia, marrow fibrosis or toxic effects on bone tissue/cells according to 65 bone biopsies taken among participants of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (66).

Teriparatide and 1-84 Parathyroid hormone

Parathyroid hormone (PTH), as the full-length human peptide or its fragments, has been extensively studied for its effects on bone. There is evidence that teriparatide (1-34 parathyroid hormone) prevents vertebral fractures (67). The evidence for preventing nonvertebral fractures is fair since a large RCT showed reduction in nonvertebral fractures (68) but two small trials did not (69, 70). In a subset of the Fracture Prevention Trial, Jiang et al. reported that teriparatide significantly increased cancellous bone volume and increased cancellous connectivity density as well as cortical thickness (71). In Europe, 1-84 PTH is available for subcutaneous daily use. An RCT showed that 1-84 PTH reduced the risk for new or worsened vertebral fracture in postmenopausal women with osteoporosis (72). Teriparatide and 1-84 PTH therapy, also because of a higher cost, are reserved for postmenopausal women with severe osteoporosis who are at highest risk of fracture. Adverse events associated with teriparatide include muscle cramps, nausea, headache, hypercalcemia, and dizziness (9), and hypercalciuria, hypercalcemia, and nausea for 1-84 PTH (72). Use of teriparatide or 1-84 PTH is not recommended in patients with hypercalcemia, bone metastases, or diseases that predispose them to bone tumors.

Strontium ranelate

This compound is licensed in Europe for the treatment of osteoporosis. While its mechanism of action has not been completely elucidated, it appears to reduce bone resorption by decreasing osteoclast differentiation and activity and to stimulate bone formation by increasing replication of preosteoblast cells, leading to increased matrix synthesis (73). The efficacy of strontium ranelate to prevent vertebral and nonvertebral fractures has been demonstrated in two large phase III double-blind, placebo-controlled trials: the Spinal Osteoporosis Therapeutic Intervention (SOTI) and the Treatment of Peripheral Osteoporosis (TROPOS) (74). Bone biopsies of lamellar bone performed in 20 postmenopausal women treated with strontium ranelate for 24, 36, or 48 months as part of the SOTI trial revealed no increase in osteoid thickness or in mineralization lag time and no decrease in mineral apposition rate (73). It is worth mentioning that strontium ranelate is the only therapy for osteoporosis with a RCT specifically designed for over 80 years old persons. This study demonstrated that therapy with strontium ranelate safely reduces the risk of vertebral and nonvertebral fractures also in the oldest old (75).

Adherence to therapy

Non-adherence to therapy is frequently observed. Studies examining patients' adherence to osteoporosis therapies report that less than half of patients who are prescribed these medications are compliant after a year (26). Such studies mainly included oral medications taken daily, weekly, or monthly. Perhaps increasing the use of once-yearly intravenous zoledronic acid would improve compliance rates. It is crucial to consider that treatment success depends not so much on the drugs available to the physicians but rather on the ability to engage the patients to adhere to the drugs prescribed. The results of evidenced-base RCTs may be translated into the community only if the adherence to therapy is similar to that in the trials.

Future molecules

Several new molecules are under development for the prevention and treatment of osteoporosis (Table 4). Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor-B ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis (76). Several new SERMs are under development, such as lasofoxifene, which has been approved by EMEA, however, it has been associated to increased incidence of venous thromboembolic events, hot flushes, muscle spasm, and vaginal bleeding (77). Odanacatib is an inhibitor of cathepsin K, an osteoclast enzyme required for resorption of bone matrix, currently under development for the treatment of osteoporosis and bone metastasis (78). Glucagon-like peptide 2 is a peptide growth factor secreted from the human intestine and potential treatment for osteoporosis due to a prevention in nocturnal bone resorption (79). Anabolic agents under development include sclerostin that mediates bone response to mechanical unloading, likely through Wnt/beta-catenin signaling (80), calcium-sensing receptor antagonists that increases PTH release (81), and activin receptor fusion protein, a bone morphogenetic protein (82).

Table 4. Future molecules

- Denosumab – monoclonal antibody against RANKL
- New SERMs
- Odanacatib – inhibitor of cathepsin K, an osteoclast enzyme required for resorption of bone matrix
- Glucagon-like peptide 2 to prevent nocturnal rise in bone resorption without affecting bone formation
- Novel anabolics:
  - Sclerostin: targets molecules involved in Wnt signaling;
  - an antagonist of the calcium-sensing receptor (CaSR);
  - an activin receptor fusion protein.

Conclusion

At present, there is high-quality evidence showing that diverse pharmacological agents decrease the risk of osteoporotic vertebral fractures (alendronate, risedronate, ibandronate, zoledronate, estrogen, raloxifene, teriparatide, 1-84 parathyroid hormone, strontium ranelate), non vertebral fractures (alendronate, risedronate, zoledronate, estrogen, teriparatide, 1-84 parathyroid hormone, strontium ranelate), and hip fractures (alendronate, risedronate, zoledronate, estrogen, strontium ranelate). It is not yet completely clear the adequate duration of treatment with bisphosphonates. While evidence for fracture risk reduction from calcium alone is less clear, it is stronger for vitamin D and calcium in combination. Oral bisphosphonates increase the risk for gastrointestinal adverse events as acid reflux that seems to be similar for all the compounds in this class. However, less frequent administration seems to decrease the possibility of these effects. Raloxifene increases the risk for pulmonary embolism and thromboembolic events. Estrogen in older women has been associated with an increased risk of dementia. Osteonecrosis of the jaw, which appears to be a class-related event, has been reported in patients with metastatic cancer under high intravenous doses of bisphosphonates and in a small subset of individuals who have been treated with bisphosphonate therapy for osteoporosis and Paget's disease of bone. The pathogenesis of this process is not yet completely elucidated. In non-oncologic patients taking oral bisphosphonates this condition is rare but the risk is uncertain and deserves careful consideration.

Even if the above-mentioned pharmacological options are available and many other molecules will be possibly available in the future, it should be remembered that nonpharmacological strategies can achieve results comparable to those of drugs. Furthermore, all RCTs of drugs for osteoporosis were associated with adequate calcium and vitamin D supplementation. Hence, pharmacological therapy should be always associated with lifestyle modifications, including a regular and moderate physical activity, a balanced diet, and the prevention of falls in the older patient.

References

1. Melton LJ, 3rd, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopa-

thy of undetermined significance. *J Bone Miner Res* 2004; 19: 25-30.
2. Mirza FS, Prestwood KM. Bone health and aging: implications for menopause. *Endocrinol Metab Clin North Am* 2004; 33: 741-59.
3. Gruntmanis U. Male osteoporosis: deadly, but ignored. *Am J Med Sci* 2007; 333: 85-92.
4. Sack F. Fighting the fracture cascade: evaluation and management of osteoporotic fractures. *Postgrad Med* 2008; 120: 51-7.
5. Rossini M, Piscitelli P, Fitto F, et al. Incidence and socioeconomic burden of hip fractures in Italy. *Reumatismo* 2005; 57: 97-102.
6. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int* 2005; 16: 581-9.
7. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004; 164: 1108-12.
8. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. *Bone* 2009; 44: 734-43.
9. North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. *Menopause* 2002; 9: 84-101.
10. Cummings SR. Prevention of hip fractures in older women: a population-based perspective. *Osteoporos Int* 1998; 8 (Suppl 1): S8-12.
11. Kannus P. Preventing osteoporosis, falls, and fractures among elderly people. Promotion of lifelong physical activity is essential. *BMJ* 1999; 318: 205-6.
12. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int* 1999; 9: 1-12.
13. Karlsson MK, Nordqvist A, Karlsson C. Physical activity, muscle function, falls and fractures. *Food Nutr Res* 2008; 52: Epub ahead of print Dec 30.
14. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 2006; 35 (Suppl 2): ii37-ii41.
15. Heinrich S, Rapp K, Rissmann U, Becker C, Konig HH. Cost of falls in old age: a systematic review. *Osteoporos Int* 2009; Epub ahead of print Nov 19.
16. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. *Osteoporos Int* 2009; Epub ahead of print Oct 9.
17. Malik P, Gasser RW, Kemmler G, et al. Low bone mineral density and impaired bone metabolism in young alcoholic patients without liver cirrhosis: a cross-sectional study. *Alcohol Clin Exp Res* 2009; 33: 375-81.
18. Stein E, Shane E. Secondary osteoporosis. *Endocrinol Metab Clin North Am* 2003; 32: 115-34, vii.
19. Pereira GA, Genaro PS, Santos LC, et al. Validation of a food frequency questionnaire for women with osteoporosis. *J Nutr Health Aging* 2009; 13: 403-7.
20. Gaffney-Stomberg E, Insogna KL, Rodriguez NR, Kerstetter JE. Increasing dietary protein requirements in elderly people for optimal muscle and bone health. *J Am Geriatr Soc* 2009; 57: 1073-9.
21. Bonura F. Prevention, screening, and management of osteoporosis: an overview of the current strategies. *Postgrad Med* 2009; 121: 5-17.
22. Bonjour JP. Dietary protein: an essential nutrient for bone health. *J Am Coll Nutr* 2005; 24: 526S-36S.
23. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr* 2002; 75: 773-9.
24. Tucker KL, Chen H, Hannan MT, et al. Bone mineral density and dietary patterns in older adults: the Framingham Osteoporosis Study. *Am J Clin Nutr* 2002; 76: 245-52.
25. Committee on School Health Pediatrics. Soft drinks in schools. *Pediatrics* 2004; 113: 152-4.
26. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009; 122: S3-13.
27. Teucher B, Dainty JR, Spinks CA, et al. Sodium and bone health: impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women. *J Bone Miner Res* 2008; 23: 1477-85.
28. Meunier PJ, Chapuy MC, Arlot ME, Delmas PD, Duboeuf F. Can we stop bone loss and prevent hip fractures in the elderly? *Osteoporos Int* 1994; 4 (Suppl 1): 71-6.
29. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev* 2002; 23: 552-9.
30. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med* 2006; 166: 869-75.
31. Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med* 2006; 119: 777-85.
32. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005; 365: 1621-8.
33. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; 370: 657-66.
34. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; 87: 1080S-6S.
35. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005; 16: 713-6.
36. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et

al. Effect of Vitamin D on falls: a meta-analysis. *JAMA* 2004; 291: 1999-2006.
37. Bischoff-Ferrari HA, Can U, Staehelin HB, et al. Severe vitamin D deficiency in Swiss hip fracture patients. *Bone* 2008; 42: 597-602.
38. Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002 23: 560-9.
39. Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. *Calcif Tissue Int* 2005; 76: 176-86.
40. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; 354: 669-83.
41. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009; 169: 551-61.
42. Kannus P, Parkkari J, Niemi S, et al. Prevention of hip fracture in elderly people with use of a hip protector. *N Engl J Med* 2000; 343: 1506-13.
43. Colon-Emeric CS, Lyles KW, House P, et al. Randomized trial to improve fracture prevention in nursing home residents. *Am J Med* 2007; 120: 886-92.
44. Kleerekoper M. Osteoporosis prevention and therapy: preserving and building strength through bone quality. *Osteoporos Int* 2006; 17: 1707-15.
45. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev* 2000; 21: 115-37.
46. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone* 2000; 27: 687-94.
47. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *Jama* 1998; 280: 2077-82.
48. Chesnut IC, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 2004; 19: 1241-9.
49. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005; 20: 2105-15.
50. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev* 2002; 23: 517-23.
51. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356: 1809-22.
52. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357: 1799-809.
53. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005; 90: 1294-301.
54. Recker RR, Lewiecki EM, Miller PD, Reiffel J. Safety of bisphosphonates in the treatment of osteoporosis. *Am J Med* 2009; 122: S22-32.
55. Migliorati CA, Schubert MM, Peterson DE. Bisphosphonate osteonecrosis (BON): unanswered questions and research possibilities. *Rev Recent Clin Trials* 2009; 4: 99-109.
56. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; 353: 99-102; discussion 99-102.
57. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA* 2001; 285: 2891-7.
58. Utian WH, Archer DF, Bachmann GA, et al. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008; 15: 584-602.
59. Banks E, Beral V, Reeves G, Balkwill A, Barnes I. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004; 291: 2212-20.
60. Eriksen EF, Langdahl B, Vesterby A, Rungby J, Kassem M. Hormone replacement therapy prevents osteoclastic hyperactivity: A histomorphometric study in early postmenopausal women. *J Bone Miner Res* 1999; 14: 1217-21.
61. Paschalis EP, Boskey AL, Kassem M, Eriksen EF. Effect of hormone replacement therapy on bone quality in early postmenopausal women. *J Bone Miner Res* 2003; 18: 955-9.
62. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators - mechanisms of action and application to clinical practice. *N Engl J Med* 2003; 348: 618-29.
63. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999; 282: 637-45.
64. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002; 87: 3609-17.
65. Grady D, Ettinger B, Moscarelli E, et al. Safety and adverse effects associated with raloxifene: multiple outcomes of raloxifene evaluation. *Obstet Gynecol* 2004; 104: 837-44.
66. Ott SM, Oleksik A, Lu Y, Harper K, Lips P. Bone histomorphometric and biochemical marker results of a 2-year placebo-controlled trial of raloxifene in postmenopausal women. *J Bone Miner Res* 2002; 17: 341-8.
67. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral

density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344: 1434-41.
68. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH. Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. *J Clin Endocrinol Metab* 2005; 90: 1583-7.
69. Kaufman JM, Orwoll E, Goemaere S, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. *Osteoporos Int* 2005; 16: 10-6.
70. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003; 18: 9-17.
71. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res* 2003; 18: 1932-41.
72. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med* 2007; 146: 326-39.
73. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004; 350: 459-68.
74. Rizzoli R. A new treatment for post-menopausal osteoporosis: strontium ranelate. *J Endocrinol Invest* 2005; 28: 50-7.
75. Seeman E, Vellas B, Benhamou C, et al. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. *J Bone Miner Res* 2006; 21: 1113-20.
76. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009; 361: 756-65.
77. Lewiecki EM. Lasofoxifene for the prevention and treatment of postmenopausal osteoporosis. *Ther Clin Risk Manag* 2009; 5: 817-27.
78. Bone HG, McClung MR, Roux C, et al. Odanacatib, a Cathepsin-K Inhibitor for Osteoporosis: A Two-Year Study in Postmenopausal Women With Low Bone Density. *J Bone Miner Res* 2009; Epub ahead of print Oct 29.
79. Wallis K, Walters JR, Forbes A. Review article: glucagon-like peptide 2 - current applications and future directions. *Aliment Pharmacol Ther* 2007; 25: 365-72.
80. Lin C, Jiang X, Dai Z, et al. Sclerostin mediates bone response to mechanical unloading through antagonizing Wnt/beta-catenin signaling. *J Bone Miner Res* 2009; 24: 1651-61.
81. Kumar S, Matheny CJ, Hoffman SJ, et al. An orally active calcium-sensing receptor antagonist that transiently increases plasma concentrations of PTH and stimulates bone formation. Bone 2009; Epub ahead of print Sept 26.
82. Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. *Growth Factors* 2004; 22: 233-41.

Accepted: December 18th, 2009
Correspondence:
Ligia J Dominguez, MD
University of Palermo
Viale F. Scaduto 6/c 90144
Palermo, Italy
Tel. 39 091 6552885
Fax 39 091 6552952
E-mail: mabar@unipa.it