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Role and Evolution of Therapeutic Options

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Introduction

Osteoporosis has been prevalent for many centuries as shown by the examination of skeletal remains [1]. The gradual ageing of the population and an age-specific increase in the incidence of osteoporotic fracture suggests that the burden of osteoporosis is increasing [2]. To date, the only cost-effective management approach to osteoporosis is primary prevention, yet many patients will present with established disease which only becomes clinically apparent after a fracture is sustained. Treatment strategies for this condition have evolved, based on both an improved understanding of the disordered pathophysiological processes and advances in pharmaceutical agents. Ideal therapies should be well tolerated, available orally, increase bone mass, restore normal bone architecture and reduce the occurrence of new osteoporotic fractures. Non-invasive measurement of bone mineral density (BMD) has allowed the response of various agents on bone to be monitored accurately, and this has been an important adjunct to the development of modern therapies.

Non-pharmacological Treatment

In the past, diagnosis of osteoporosis was clinically based, being at the time of a fragility fracture. In the acute event, the aim of management was to minimize pain and discomfort, reduce and fixate the fracture and, it was hoped, thereby restore full function. This approach is still utilized for fractures of both the hip and the wrist. Early treatment of spinal fractures used to consist of wearing corsets or surgical spinal braces, but this practice has become outdated and mobilization through active physiotherapy is now encouraged soon after the acute event. Analgesia can also be provided by simple analgesics, acupuncture, transcutaneous nerve stimulation (TENS) and injectable calcitonin.

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Calcium and Vitamin D

Adequate calcium and vitamin D nutrition is essential for the development and maintenance of a normal skeleton. In view of their important role in bone homeostasis, calcium and vitamin D have been widely used in the treatment of osteoporosis for many years, although conflicting results have been obtained between studies.

Calcium appears to have little effect if given within the first 5 years of the menopause when bone loss is predominantly due to oestrogen withdrawal [3]. Calcium supplements have, however, been shown to reduce age-related bone loss in prospective controlled trials by up to 50% [3,4]. A retrospective case-control study has also shown a significant effect of calcium supplements on the risk of hip fracture [5], although data from controlled clinical trials have not yet been obtained. At present, calcium supplements are often administered as a combined therapy with other agents for the treatment of osteoporosis.

The theory underlying the early treatment of osteoporosis with vitamin D was that vitamin D acted to increase calcium absorption in the gastrointestinal tract and thereby inhibited parathyroid hormone (PTH)-mediated bone resorption. Analogues of vitamin D have also been examined to see whether they have increased efficacy in the treatment of mild to moderate osteoporosis [6,7]. Calcitriol (0.25 μg twice daily) reduced the rate of new vertebral fractures, compared with calcium (1 g), during the second (9.3 vs 25.0 fractures per 100 patient-years) and third years (9.9 vs 31.5 fractures per 100 patient-years) of the study [7]. Peripheral fractures were also reduced in the calcitriol group compared with the calcium-treated group (11 vs 24 fractures). Toxicity is a concern with vitamin D analogues because of hypercalcaemia and hypercalciuria, but the incidence of adverse events reported in the literature is low (<5%). These can be minimized by monitoring calcium intake, omitting calcium supplements, measuring urinary calcium excretion, increasing water intake and administering vitamin D twice daily.

Supplementation with 1.2 g/day elemental calcium

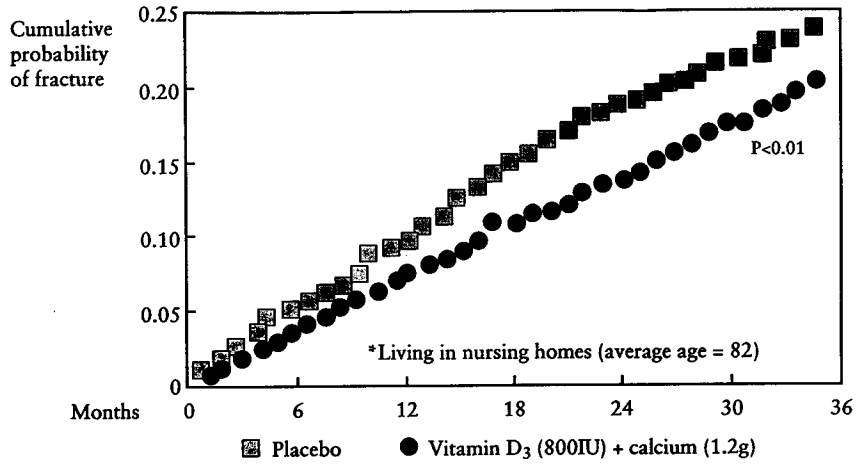

Fig. 1. Effect of vitamin D_3 (800 IU/day) and calcium (1.2 g/day) on the cumulative probability of hip fracture in the elderly. (Reproduced with permission from Meunier PJ et al. Osteoporosis Int 1994 (Suppl 5B):S71.)

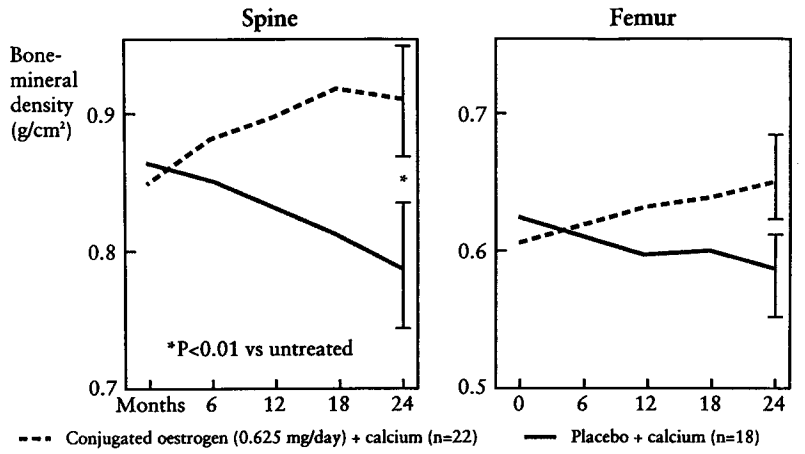

Fig. 2. Effect of conjugated oestrogen (0.625 mg/day) on bone mineral density in postmenopausal women with osteoporosis. (Reproduced with permission from Lindsay R, Tohme JF. Obstet Gynecol 1990;76:290.)

and 800 IU/day cholecalciferol has recently been shown to reduce the risk of hip fracture and other non-vertebral fractures in an elderly nursing home population (Fig. 1) [8].

Hormone Replacement Therapy

The association between osteoporosis and oestrogen was first described by Fuller Albright in 1941 when he noted that 40 of 42 women with osteoporotic fractures were postmenopausal [9]. Subsequently the associations between oophorectomy and accelerated bone loss, and the beneficial effects of oestrogen, were observed (Fig. 2) [10]. Given the central role of oestrogen, deficiency in the development of osteoporosis, treatment regimens to reduce fractures have focused on replacement therapy with ovarian hormones (HRT). Several regimens and routes of administration are available and appear capable of inhibiting bone loss, but to date none of these fully mimics the pattern of hormone release in premenopausal women. In women with established osteoporosis, oestrogen given with or without a progestogen has been shown to increase bone mass at the spine, forearm and total skeleton [10–12].

A large amount of epidemiological data supports a reduction in fracture risk at the hip and forearm for those treated with oestrogen and oestrogen/progestogen combinations, whereas fewer data are available for vertebral fractures. The protective effect against hip fractures is considerable, with most studies showing a 50%–70% risk reduction in oestrogen users. The minimum duration of therapy required for protection against hip fracture is controversial. Cross-sectional studies suggest a duration of oestrogen therapy of 5–10 years for an effect on hip fracture, although whether this positive effect extends after the age of 75 years in past users is debated [13]. This is of obvious importance as the incidence of hip fracture is high in women of this age, and prolonged therapy (i.e. life-long) may be required to protect women fully into later life when their risk of fracture is highest. With treatment of this duration, compliance will be also a major issue. Studies have shown that 40% of women prescribed HRT are not compliant at 1 year; in many instances the return of menstrual bleeding is cited as a major reason for discontinuing treatment. A further concern affecting long-term compliance with prolonged treatment with HRT is that the risk of breast cancer appears to be increased with use of HRT for more than 5 years [14,15].

There is much recent interest in non-bleed preparations of HRT (hormone-based treatments which do not induce menstrual bleeding) such as continuous and

combined HRT [12] and synthetic analogues [16], although the long-term effect of these agents on cardiovascular risk and serum lipid profiles is as yet unknown and further data are awaited. Oestrogen antagonists, which have positive skeletal, as well as anti-lipid and anti-breast cancer effects, with few adverse effects on the endometrium, are also currently under clinical investigation and may prove effective in treating established disease.

Anabolic Steroids

As the incidence of osteoporosis is lower in males, it was thought that the male sex hormones may offer protection. Treatment with testosterone derivatives is obviously not suitable in female patients, yet anabolic steroids derived from 19–norethisterone are thought to be effective in preserving BMD, acting through a decrease in bone turnover. Their effect on BMD can be explained in part by the increase in muscle mass and reduction in body fat which accompanies treatment [17], which may have beneficial effects on muscle strength, thereby reducing the incidence of falls and possible fracture. The long-term use of anabolic steroids in the treatment of osteoporosis is probably limited, however, by the associated side-effects such as an adverse effect on high density lipoprotein cholesterol, hoarseness and virilization which are not negated by parenteral administration.

Calcitonin

Calcitonin is an endogenous peptide of 32 amino acids which possesses anti-osteoclastic activity. In clinical practice, four calcitonins (human, pig, salmon, eel) have been used in studies of osteoporosis. Parenteral administration of calcitonin is given by either subcutaneous injection, suppository or nasal spray.

A number of small studies have shown a positive effect of parenteral calcitonin on bone mass in postmenopausal osteoporosis, this effect being most marked at axial sites and in those with high bone turnover [5,18]. Calcitonin has also been shown to have analgesic properties, which make it suitable for use in those with pain secondary to vertebral collapse, particularly in the acute state. The physiological mechanisms underlying this action are poorly understood.

Long-term administration of subcutaneous calcitonin appears safe and is not associated with any long-term side-effects. The nasal spray often causes minor problems, particularly nasal irritation and discharge. The effect of calcitonin appears to wane with time; the mechanism of this is unclear. Antibody formation can occur with use of non-human calcitonin and this can result in minor allergic reactions and resistance to treatment. Resistance to salmon calcitonin appears less frequent if it is given in low doses, intermittently and via the intra-nasal route. Problems of resistance and the costs of long-term therapy with the nasal spray are likely to limit its use to the short term.

Fluoride

Fluoride was first recognized as a bone growth stimulator over 30 years ago and sodium fluoride (NaF) and sodium monofluorophosphate (Na_2PO_4F) have been licensed for the treatment of osteoporosis in many European countries.

Fluoride treatment has been shown to produce a linear increase in vertebral bone mass of 4%–8%/year, although up to 40% of patients show no significant response. The effect of fluoride on the frequency of new fractures is controversial and dependent on the dose and formulation of the fluoride salt [19–21]. Most studies have not shown increases in bone density at the cortical sites of the forearm or femoral neck, and there is concern that fluoride treatment may actually increase the risk for hip fracture. Slow-release sodium has recently been shown to inhibit new vertebral fractures in patients without prevalent fractures and to increase BMD at the lumbar spin and femoral neck [22].

Fluoride salts have a narrow therapeutic window and the exact formulation and dosing schedule have yet to be determined. Impaired mineralization can occur with NaF at daily doses of 20–40 mg, although this can be overcome with concurrent administration of calcium supplements. Side-effects are not uncommon, particularly gastrointestinal and the lower extremity pain syndrome. The latter occurs in 15%–20% of patients, is dose related, and probably represents the healing of stress microfractures. Fewer side effects are noted with the use of low dosages of sustained release preparations and with use of sodium monofluorophosphate.

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate, an endogenous substance which inhibits the mineralization of bone. They contain a nonhydrolysable P–C–P bond and have two side chains, one that participates in binding to bone and one that determines the pharmacological properties of the drug. Cyclical intermittent etidronate has been shown to increase spinal BMD in placebo-controlled studies (Fig. 3) [23,24]. Despite certain limitations regarding the power of these two studies, the combined results suggest that this regimen of etidronate therapy is effective in reducing further vertebral fractures in patients with severe osteoporosis and possibly accelerated bone loss. In the UK, etidronate is indicated for cyclical use in the treatment of established vertebral osteoporosis.

Unlike etidronate, newer bisphosphonates produce little or no inhibition of mineralization at doses that show anti-resorptive activity, and are suited to continuous, daily administration. Treatment with tiludronate for 6 months caused a mean increase in spinal bone mass

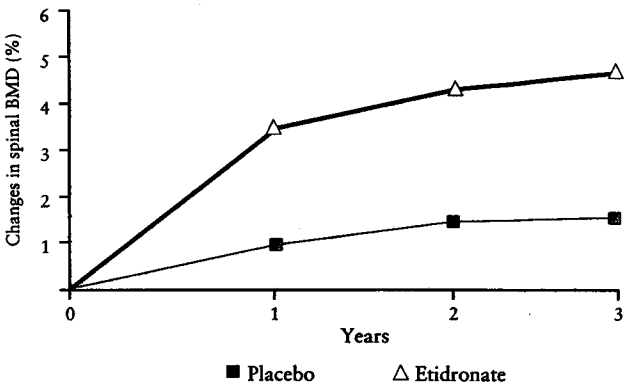

Fig. 3. Effect of etidronate (treatment cycle of etidronate 400 mg/day for 14 days followed by calcium 500 mg/day for 74 days) on spinal bone mineral density in postmenopausal women with osteoporosis (n = 423). (Adapted from Harris ST et al. Am J Med 1993;95:557.)

of 1.33% which was preserved over 2 years [25]. Alendronate treatment for 3 years in a study of 994 postmenopausal women with osteoporosis (i.e. BMD 2.5 SD below the young adulthood peak value) caused significant increases in BMD of 2.2–8.8% at all skeletal sites, the effect being the most marked at the spine [26].

Parathyroid Hormone

Treatment with the 1–34 fragment of PTH has been evaluated as an anabolic agent in osteoporosis. Although high plasma concentrations of PTH stimulate bone resorption, PTH may stimulate bone formation when given intermittently at low doses.

Studies indicate an increase in cancellous bone mass with treatment with PTH (1–34), although there appears to be a redistribution from cortical bone [27,28]. In an attempt to reduce this cortical loss, concurrent treatment with active vitamin D metabolites or oestrogen replacement therapy has been assessed whilst using PTH. Current data suggests that the anabolic effect may plateau after several years and the exact therapeutic regimen has still to be determined. At present no long-term data on PTH therapy and vertebral fracture incidence are available.

Ipriflavone

Flavanoids are naturally occurring plant metabolites, and ipriflavone belongs to the isoflavone class, a group that has weak oestrogenic properties. At present ipriflavone is licensed for the treatment of osteoporosis in only a few countries worldwide. Studies have suggested an increase in forearm bone mass and prevention of spinal bone loss, but no fracture prevention data are yet available [29].

Future Agents

A growing number of new and novel treatments are emerging. Bone cells synthesize a large number of growth factors which enhance osteoblast proliferation. Various growth factors, such as insulin-like growth factors 1 and 2 and transforming growth factor beta, have been isolated, and are now available as potential treatment agents. Other compounds such as strontium salts and silicon derivatives are undergoing preclinical and clinical trials and may also soon be available for the treatment of established osteoporosis.

Conclusions

The incidence of osteoporosis has increased over the last 30 years, and is expected to continue to increase into the next century. Drug treatment for this condition has evolved with an understanding of the disordered processes that underlie the development of low bone mass and fracture. At present, a number of different drugs can be used safely with the expectation of preventing an initial or subsequent osteoporotic fracture. HRT remains the mainstay of treatment, although many women receive therapy for a time period that is insufficient to have any major impact on fracture risk. It is likely that non-bleed preparations and oestrogen antagonists will be used widely in the future in an attempt to improve compliance, although concern will still exist about the long-term safety of these therapies. New bisphosphonates appear good alternatives for women who are unable or unwilling to take HRT. Data from clinical trials in progress with these agents are eagerly awaited to assess their impact on hip fracture prevention. Other therapies under investigation will also soon be available for treatment in the clinical setting. Exactly who will benefit from a particular therapy, the duration of treatment and the use of combinations of bone-forming and anti-resorptive agents are the challenges for the next decade.

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