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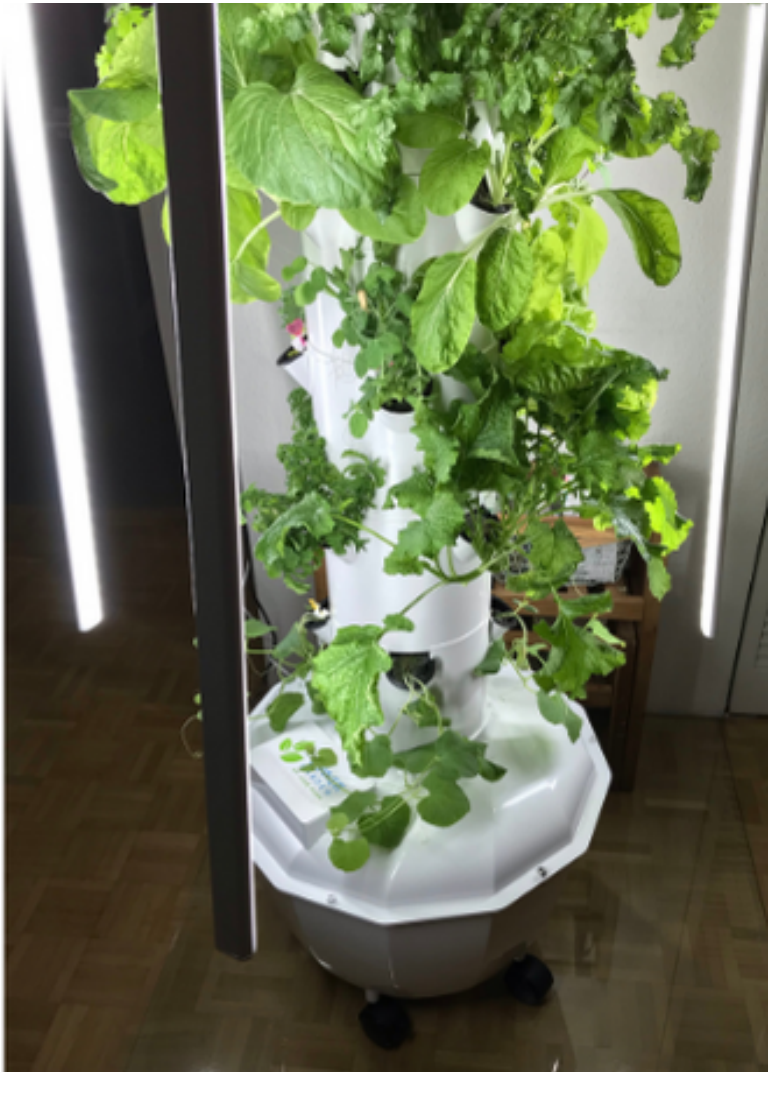

P. Burckhardt

TREATMENT OF OSTEOPOROSIS TODAY AND TOMORROW: AN OVERVIEW

THE CONVENTIONAL DRUGS

The *conventional treatment* relies on either antiresorptive drugs (bisphosphonates such as alendronate, risedronate, and calcitonin), or osteoblast stimulating drugs (fluorides), associated with calcium, and increasingly also with vitamin D, the latter being often deficient even in healthy younger subjects. In postmenopausal women, hormone replacement therapy (HRT) is either added, or serves itself as treatment. Limiting facts of these treatments are the following: fluorides could not decrease fracture incidence, oral bisphosphonates are often interrupted for gastric intolerance, and HRT raises the fear of breast cancer and of bleeding. In the average, fracture risk can be reduced by 30–50 % after 2 to 5 years, whatever treatment used. Not only these treatments are of limited average efficacy, they are in part also characterized by high numbers of patients to treat for avoiding one fracture, especially hip fractures. E.g., almost 100 patients with high risk of fracture have to be treated with bisphosphonates for 3 years, in order to prevent one single hip fracture.

Which improvements can be expected with the already known and the conventional drugs?

First, the *new bisphosphonates,* e.g., ibandronate, zoledronate, will hardly be more effective than those already used. The higher doses which have to be taken only once a week might improve compliance. Second, the *intravenous administration of bisphosphonates,* already tested with many of them, especially with ibandronate, which needs only a few doses per year, might show even better compliance. But the effect on fracture incidence will probably not be better than that obtained with the oral route of administration.

New data on the use of *low dose estrogens* show, that with roughly half the dose of estrogens than those used in HRT, there is still a clear cut effect on bone mineral density, enough to be used in the prevention and treatment of osteoporosis. Although less effective than the doses used in conventional HRT, low dose estrogen treatments seem to have a better effect on bone than first pretended. E.g., while 2 mg of β-estradiol lead to the known increase of BMD, 1 mg still prevented postmenopausal bone loss, all patients showed either no loss or a small rise in BMD [1]. The new preparations of low dose continuous-combined HRT, which obviously have less side effects and a lower risk profile than conventional HRT, can be given to elderly osteoporotic patients and might be especially appropriate for combined treatments.

Higher efficacy can be expected from the *combination of drugs.* Synergistic effects have been shown with the combination of monofluorophosphate and HRT [2], but also with bisphosphonates [3] or calcitonin combined with HRT. PTH too has been tested in combination with estrogens [4], and also with bisphosphonates, as well as fluoride with bisphosphonates [5]. But despite their high potential for therapeutic improvement, combined treatments have yet been insufficiently tested.

Sequential treatments, so far untested, also might increase the efficacy of already known drugs. E.g., stimulation of bone formation with fluorides or PTH could be followed by antiresorptive treatments, i.e., bisphosphonates, as successfully demonstrated in rats [6].

NEW DRUGS

Hormonal treatments of postmenopausal osteoporosis can be improved by new classes of estrogen-derived substances, the SERMS, esp. raloxifen [7], and *tibolone* [8]. Both were shown to be effective in treating and preventing osteoporosis. They might replace conventional HRT in the prevention and the treatment of osteoporosis. Both increase BMD, decrease fracture risk, and avoid bleeding and the breast cancer risk. By this, they not only can be given to patients with a history of breast cancer and with intolerance of estrogens, it will be acceptable for all patients and physicians who fear an increased risk of breast cancer. In addition, it will become easy to combine bisphosphonates, fluoride, and calcitonin with SERMS or with tibolone, and to increase by that the efficacy of the conventional treatments. A result of recent discoveries, statins, resp. HMG Co-A reductase inhibitors, well known and widely used, seem to prevent osteoporosis in humans as agonists of bone formation [9].

Which are the new drugs in development?

As *bone forming agents, PTH and PTH analogues* showed various positive effects in animals. PTH 1-34 was effective in glucocorticoid-induced osteoporosis [10] and in postmenopausal women [4]. In combination with estrogens, PTH achieved an increase of BMD of about 30 % in lumbar spine and of over 10 % at the femoral neck in 2 years [11], an effect which has never been reached with the actual treatments. PTHrP analogue increased lumbar BMD by almost 10 % in 6 months only [12]. But if these outstanding efficacies will be exploited for the development of commercially available drugs, is still open.

Growth hormone, although efficacious in animal models, did not yet show positive effects on BMD in the human. The oral GH secretagogue MK-677 increased bone formation in obese males [13]. RhIGF-I/IGFBP3 (*somatokine*) stimulated bone metabolism in elderly women [14]. More simple, *strontium* ranelate, which stimulates bone formation and also inhibits bone resorption, increases BMD, and was effective in the treatment of vertebral osteoporosis [15]. High expectancies are placed into the *bone morphogenic proteins,* which promote cell differentiation into osteoblasts, and showed positive effects on bone in animals.

As *inhibitors of bone resorption, osteoprotegerin,* a novel TNF-receptor family member, which diverts the RANK ligand which is essential for osteoclast recruitment and activity, profoundly inhibits endosteal bone resorption in the animal and recently also in postmenopausal women [16] and might offer new possibilities. *Inhibitors of cathepsin K,* produced by the osteoclasts, prevent bone resorption in the rat. *Inhibitors of the metalloproteinases,* produced by the osteoclasts for degradation of the bone matrix, are also promising. But although tested since many years in basic research, they are not yet brought to the level of clinical testing.

Last newcomer, the *gene therapy,* offers new possibilities, e.g., the suppression of osteoclasts by epidermal growth factor receptor induced by adenovirus into osteoclasts, so far tested in animals. Stimulation of bone formation could be achieved in basic research by introducing mineralization protein LIM-1 into bone marrow [17], or BMP-7 into gingival fibroblasts [18], or plasmid expression vector delivery of fibroblast growth factor into bone marrow [19]. The application of these techniques to human medicine still requires more research.

More pragmatic, prevention of falls, which are as responsible for hip fractures as osteoporosis, should be improved, appropriate physical exercises promoted and hip protectors more often used. The latter showed to be highly effective when applied in elderly residents of homes.

Conclusion

The actually available drugs are of restrictive efficacy. Spectacular increases of BMD were achieved with PTH and analogues, but their introduction into the market is yet uncertain. New substances are in development for inhibiting bone formation, and also for stimulating bone formation. Osteoprotegerin already showed high efficacy in humans. Until several of these new drugs arrive to clinical application better use of the known drugs is advised, by exploiting the possibility of combined and sequential treatments. Non-pharmacological interventions need to be tested more seriously and might get more attention.

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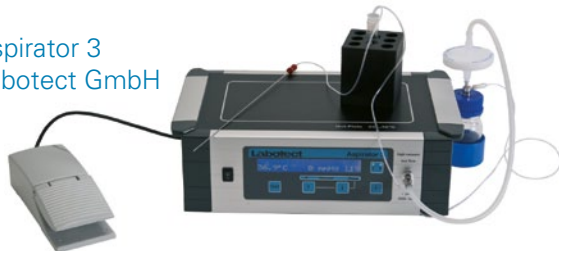

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