Fluoride in the prevention and treatment of glucocorticoid-induced osteoporosis

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ABSTRACT

Since the use of fluoride has been shown to stimulate bone formation and since decreased bone formation is a key feature in the pathogenesis of corticosteroid-induced osteoporosis (CIOP), fluoride is, at least theoretically, attractive for the prevention and treatment of CIOP. In postmenopausal women positive effects of low-dose fluoride on the bone mineral density (BMD) of the lumbar spine and on the vertebral fracture rate were found; in contrast, in patients treated with high dose fluoride, an increase in the peripheral fracture rate was found. Randomized controlled trials of the effects of fluoride in Cs-treated patients are scarce. Although positive effects of low-dose fluoride on BMD of the lumbar spine have been observed, fluoride does not represent the first choice therapy for the prevention or treatment of CIOP, because no positive effects on BMD of the hips and (so far) no reduction in the vertebral fracture rate have been shown.

Introduction

In order to understand the rationale for the use of fluoride in corticosteroid (Cs)-treated patients, the pathogenesis of corticosteroid-induced osteoporosis (CIOP) and the effects of fluoride on bone (metabolism) will be briefly discussed. Since data on the effects of fluoride in the prevention and treatment of CIOP are scarce, we will first go into the results of studies with fluoride in postmenopausal women, and will then discuss the available data on the effect of fluoride in the prevention and treatment of CIOP.

Effects of corticosteroids on bone

Although it is well known that the use of corticosteroids (Cs) is associated with osteoporosis (1-3), the pathogenesis of CIOP has not fully been elucidated. Before discussing the mechanism of CIOP, it is important to realize that in healthy adults bone remodelling is a continuous process, in which osteoblastogenesis and osteoclastogenesis are tightly coupled (4). Bone morphogenetic proteins provide the tonic baseline control of both processes, which may be influenced by other inputs (e.g. hormones, disease activity, mechanical strain).

In histomorphometric studies, a reduced thickness of osteoid seams and decreased calcification rate, measured by tetracycline labeling, have been shown during treatment with Cs (5), which indicates that bone formation is inhibited during treatment with Cs. Recently, it also has been shown that Cs not only have a suppressive effect on osteoblastogenesis, but also promote the apoptosis of osteoblasts and osteocytes (4).

Biochemical markers are very suitable to measure changes in bone metabolism. In a study in healthy volunteers, it was observed that Cs, even when used in low dosages, e.g. 10 mg prednisone/day, may have an inhibiting effect on bone formation (6).

Data on the influence of Cs on bone resorption are somewhat conflicting. In histomorphometric studies, the number of osteoclasts and erosion depths were increased, indicating that bone resorption is stimulated in Cs-treated patients (5). Increased bone resorption can be related not only to the use of Cs, but also to the underlying disease: e.g. in active RA bone resorption is increased (7). Without interference of the underlying disease, in a study in healthy volunteers, urinary excretion of pyridinolines (markers of bone resorption) was unchanged or even slightly decreased in Cs-treated patients (6).

Thus, these data suggest an uncoupling in Cs-treated patients between bone formation (decreased) and bone resorption (absolutely or relatively increased); the most important effect of the use of Cs seems to be the inhibition of bone formation.

Effects of fluoride on bone

At the molecular level, it is suggested

that fluoride inhibits a unique fluoride-sensitive phosphotyrosine phosphatase (PTP) in osteoblasts, resulting in an increase in the tyrosine phosphorylation level key signaling proteins of the MAPK mitogenic transduction pathway, thus potentiating the bone cell proliferation initiated by growth factors (8).

In general, studies in which fluoride was used in one of the treatment arms have shown a strong positive effect on the bone mineral density (BMD) of the spine, while the effects of fluoride at more cortical sites (e.g. the hips) are much smaller (9, 10). It is thought that this difference is related to the fact that the spine largely consists of trabecular bone, which is highly active metabolically, while bone turnover is much slower at more cortical sites.

Effects of fluoride in patients not treated with corticosteroids.

Since data on the effects of fluoride in the prevention and treatment of CIOP are limited, it is useful to summarize the data on the use of fluoride in postmenopausal (not Cs-treated) osteoporotic women. In the 1980s, an increase in BMD of the lumbar spine and a decrease in the vertebral fracture rate were observed in patients treated with 40-60 mg sodium fluoride daily (11,12). In another study (13), an increase in the BMD of the lumbar spine was accompanied by an increase in the number of peripheral fractures. In the last study, the fluoride dosages were probably too high: 60 and 90 mg on alternating days. Moreover, the fluoride was not given in the form of enteric-coated tablets, probably leading to high (toxic) peak serum levels of fluoride (13).

Thus, data on the effects of fluoride on fractures are conflicting: both decreased and increased fracture rates have been observed. It is suggested that high dosages of fluoride may (over)stimulate bone formation, resulting in a large increase of BMD that is not associated with an increase in bone strength (or bone quality); on the contrary, bone quality may even be decreased in patients treated with high dose fluoride.

An important side effect of fluoride in patients treated with high dosages of fluoride are incomplete fractures, which occur almost entirely in the weight-bearing bones, and which resemble the stress fractures caused by skeletal overload in athletes (13).

Gastrointestinal symptoms are also important side effects of sodium fluoride; it is thought that these symptoms are elicited by a direct irritating effect of fluoride on the gastric mucosa. Gastrointestinal side effects occur less frequently when enteric-coated sodium fluoride tablets or monofluorophosphate are used.

In a recent study (14), Ringe *et al.* compared the effects of low dose intermittent monofluorophosphate (11.2 mg fluoride/day) with continuous (high dose) monofluorophosphate (20 mg/day) and with calcium alone: the incidence of new vertebral fractures per 100 years of treatment was 8.6, 17.0 and 31.6, respectively. The same continuous regimen of fluoride treatment was used in another study (15), in which new vertebral fractures were observed in 2.4% and 10% of patients treated with monofluorphosphate or calcium (only), respectively. These results not only indicate that fluoride has a preventive effect on fractures in postmenopausal osteoporotic women, but also illustrate that low dose fluoride may be more effective than high dose fluoride in the prevention of osteoporotic fractures.

Thus, there seems to be a narrow therapeutic window for fluoride, since the efficacy and side effects are both dose-related. Obviously, this is a limiting factor for prescribing fluoride, especially in elderly patients with osteoporosis, in whom deterioration of kidney function may elevate blood levels of fluoride.

In conclusion, prescribing low dose fluoride seems to be safe, and may have positive effects on bone; on the contrary, prescribing high dose fluoride may be associated with side effects and may even increase the fracture rate.

Effects of fluoride in the prevention and treatment of corticosteroid-induced osteoporosis

On the one hand, it appears to be adequate to use anti-osteoporotic drugs, e.g. bisphosphonates, in Cs-treated patients, based on randomized clinical trials in which a bone sparing effect has been demonstrated (16-18). On the other hand, it seems attractive to use drugs based on the pathophysiology of the underlying disease and the molecular mode of action of the prescribed drugs.

As described, the pathogenesis of Cs-induced osteoporosis is different from that of postmenopausal osteoporosis. In postmenopausal osteoporosis, bone resorption and, to a lesser degree, bone formation are generally increased, so that anti-resorptive therapy (e.g., with bisphosphonates) seems to be a logical strategy.

In contrast, fluoride could be effective against Cs-induced osteoporosis, since the inhibition of bone formation plays a major role in the pathogenesis of Cs-induced osteoporosis (4-6) and since fluoride is the only available pharmacologic agent that has been consistently shown to stimulate osteoblast activity and bone formation (10).

The positive effects of fluoride on BMD in Cs-treated patients have been assessed in retrospective, open and non-randomized trials (19-22). In a retrospective study in which 13 Cs-treated patients were taking fluoride (40-60 mg/day sodium fluoride), bone mineral mass measured by neutron activation analysis increased from 0.65 to 0.81 after 4 years (19). In an open study of 19 Cs-treated patients, the mean increase in BMD at the lumbar spine was 18.7% after 14 months of treatment with 20-30 mg slow-release fluoride per day (20).

In an open study in 48 patients, the effect of monofluorophosphate (26 mg/day of fluoride) was compared with that of calcium alone (control group). After 18 months, BMD had increased by +7.8% in the fluoride treated patients versus +3.6% in the control group (21).

In another study (22) on Cs-treated patients, the effect on BMD of monofluorophosphate supplemented with calcium and vitamin D (group 1, n = 8 patients) or of calcium and vitamin D alone (group 2, n = 7 patients) was compared with the BMD in 14 renal transplant patients who were not on any specific treatment (group 3, historical controls). No significant changes in BMD were observed at the hips, while lumbar BMD tended to rise in groups 1 and 2, and to decrease in group 3, leading to a statistically significant difference between groups 1 and 3

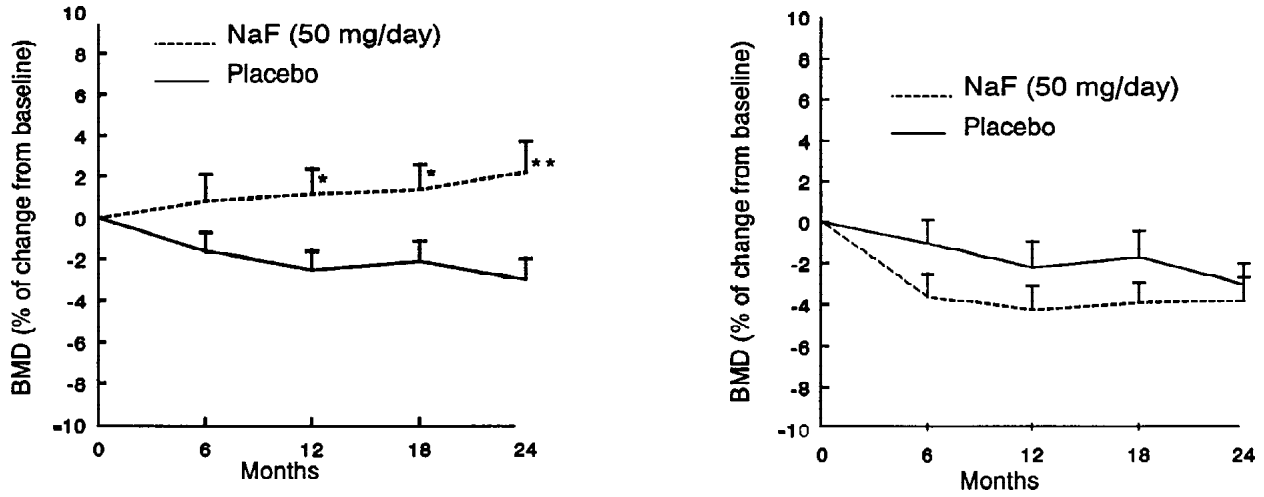

Fig. 1. Effect of fluoride (NaF) compared with that of placebo on bone mineral density (BMD) of the lumbar spine (**a**) and hips (**b**) in corticosteroid-treated patients without established osteoporosis. * $p < 0.05$ difference in the changes in BMD between groups; ** $p < 0.01$ difference in the changes in BMD between groups.

($p < 0.05$).

In a randomized, double-blind study on patients with Cs-treated respiratory diseases in which 28 patients were enrolled, a comparison was made between the effects of 100 mg monofluorophosphate plus calcium versus calcium alone. There was a statistically significant difference in the change in BMD of the lumbar spine between the two groups after 2 years ($p < 0.05$); the increase in BMD in the fluoride group was 11% (23).

We performed two randomized trials in which the effect of low dose fluoride in Cs-treated patients was studied (24, 25). The primary endpoint in both trials was the difference in the change in BMD of the lumbar spine; neither trial was large enough to observe a difference in the fracture rate between patients who were treated with fluoride and those who were not. The two trials differed from each other in terms of the presence or absence of vertebral deformities at baseline. In the first study (24), which was a randomized, double-blind placebo-controlled trial, 44 Cs-treated patients without vertebral fractures were enrolled in a 'prevention-study'. The effects of low dose sodium fluoride (25 mg twice daily) were compared with that of placebo: after 2 years, the difference in the change in BMD at the spine between the two groups was +5.2% (95% CI: +1.8% to +8.6%; $p < 0.01$), and at the hips +0.8% (95% CI: -2.1% to +3.8%) (Figs. 1 and 2).

We concluded that, in Cs-treated patients without established osteoporosis, fluoride prevents bone loss in the lumbar spine but does not have a positive effect on the BMD of the hips.

We also investigated whether the administration of low dose fluoride in addition to cyclical etidronate has a positive effect on BMD in patients with established osteoporosis during continued treatment with Cs (25). Forty-seven Cs-treated patients were included in this 2-year randomized, double-blind, placebo-controlled trial. Established osteoporosis was defined as the presence of one or more vertebral (osteoporotic) deformities on radiographs. All patients were treated with cyclical etidronate, calcium and either sodium fluoride (25 twice daily) or placebo. After 2 years of treatment, the BMD of the lumbar spine in the etidronate/fluoride group had increased +9.3% (95% CI: +2.3% to +16.2%, $p < 0.01$), while the BMD in the etidronate/placebo group was unchanged: +0.3% (95% CI: -2.2% to +2.8%).

For the hips, no significant changes in BMD were observed in the etidronate/fluoride group after 2 years: -2.5% (95% CI: -6.8% to +1.8%), while in the etidronate/placebo group the BMD had significantly decreased: -4.0% (95% CI: -6.6% to -1.4%; $p < 0.01$).

We concluded that the effect of combination treatment with fluoride and etidronate on the BMD of the lumbar spine in Cs-treated patients with established osteoporosis is superior to that of etidronate alone (Fig. 3).

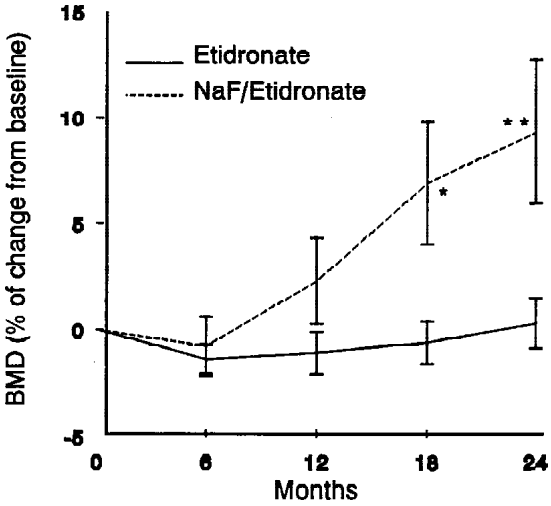

Fig. 2. Effect of fluoride (NaF)/etidronate compared with that of placebo/etidronate on bone mineral density (BMD) of the lumbar spine in corticosteroid-treated patients with established osteoporosis.
* $p < 0.05$ difference in the changes in BMD between groups; ** $p < 0.01$ difference in the changes in BMD between groups.

Conclusion

Although the use of fluoride is theoretically attractive in Cs-treated patients and although it has been shown that fluoride, prescribed for the prevention and treatment of CIOP, increases BMD of the lumbar spine, it cannot be considered the first choice for these indications because, in contrast to therapy with bisphosphonates, no positive effects on BMD of the hips and (thus far) no reduction in the vertebral fracture rate have been shown.

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