Use of Alendronate in treatment of secondary osteoporosis from hypopituitarism: a case report

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Abstract. - The authors report a case of hypogonadotropic and hypothyrotropic partial hypopituitarism, being treated for over sixteen years with a substitution therapy consisting of estroprogestogen hormones and L-thyroxine, presenting severe secondary osteoporosis, detected by densitometric examination (DEXA) of the medial and ultradistal sites of the non dominant radius. The patient was treated with alendronate (10 mg/die) for two years, in addition to the estroprogestogen therapy, resulting in a significant recovery of bone mass, equal to 16% compared to initial values, reaching near normal bone density values. On analysing the mechanisms of action of the bisphosphonates, the estrogens and the L-thyroxines, the authors suggest a synergic mechanism between the estrogen and the alendronate, which act on the bone turn-over at different times. Also, the alendronate would seem to antagonise the osteopenia of L-thyroxine, though this mechanism is still unknown.

Key Words: 
Hypopituitarism, Osteoporosis, Alendronate, Estrogens, L-thyroxine.

Introduction

Osteoporosis is a common pathology in the female sex; it is progressive and disabling and its main clinical manifestation consists of fractures above all of the hip bone, the distal radius and the backbone. Osteoporotic fractures are certainly multifactorial in etiology, however the most important pathogenic role can be assigned to the reduction in bone mass and the consequent increase in skeletal fragility. There is obviously no bone mass level that can be associated to a zero fracture risk, however a suitable analogy would be the association between cholesterol and coronary diseases; there is an exponential increase in fracture risk as bone density diminishes.

Various epidemiologic trials have revealed that a drop in bone density equal to standard deviation with respect to mean premenopausal values is associated to a two-fold increase in fracture risk. This poses the problem of preventing and treating osteoporosis to reduce this risk, thereafter assessing whether the changes in bone density induced by the treatment represent a true reduction in the risk. That is to say that the efficacy of the treatment must be proven statistically and clinically, considering that early increases in bone density, even modest, and their maintenance, will result in progressively better results over time, particularly if the newly formed bone is qualitatively normal on histological examination and significatively resistant. In prevention particular attention should be dedicated to the two primitive forms of osteoporosis; senile and post-menopausal, and to secondary osteoporosis that occurs at early age from, for example, hypogonadism or iatrogenesis (glucocorticoids, L-thyroxine, etc.).

Clinical Case

Young woman suffering from secondary osteoporosis due to hypogonadotropic and hypothyrotropic partial hypopituitarism.

F.A., a female nurse aged 39, is admitted to the Institute of Medicine after accidentally inhaling toxic insecticide substances.
The pathological history revealed that the patient suffered from hypogonadotropic and hypothyrotropic partial hypopituitarism since the age of 23, due to selective adenohypophysis following trans-sphenoidal adenomectomy (PRL-HGH-secreting acidophilic microadenoma). After surgery the presence of transient diabetes insipidus was treated with desmopressin and hypogonadism and hypothyroidism have been treated with substitutive therapy ever since, respectively consisting of estroprostogens (conjugate estrogens-Premarin-0.625 mg, one tablet/die for 21 days and medroxyprogesterone acetate-Farlutal-5 mg from 16th to 21st day of each month, over the last eight years estradiol - E piestrol - crt 50 and novmegestrol - Lutenyl – 5 mg) and L-thyroxine (Eutirox 100-125 µgr/die). Moreover, the patient had been administered cortisone for an unspecified period (Cortone acetate) and ACTH-like (Synacten Depot).

The family history was positive for ischemic cardiopathy, diabetes and dyslipemia.

On physiological examination the patient reported being a good eater (present weight 60 kg, height 160 cm), that she had never drunk alcohol or coffee, and that she had never smoked.

Physical examination: nothing to remark.

During her stay in hospital a number of clinical-diagnostic examinations were performed: routine blood tests revealed only a slight rise in the cholesterol level (269 mg/dL). A chest x-ray revealed a round shape with regular borders in left suprabasal retrosternal region that required further investigation by CT. A n encephalo CT examination for sella turcica presented no morph-structural alterations in the sella region (apart from those arising from the previous surgery), nor alterations to the cerebral and cerebellar parenchyma. The thyroidal hormone profile was well balanced, whereas the sexual hormone values, at the lowest limit for normal, were compatible with the patient’s clinical condition (Table I). As the patient belonged to a risk category for secondary osteoporosis (hypogonadic, iatrogenous), she underwent a mineralometric examination using the DEXA method on the ultradistal and mediodistal sites of the non-dominant sites which revealed the patient to suffer serious osteopenia, bordering on frank osteoporosis, with a bone mineral density (BMD) of 289 mg/cm² and a T score of -2.40. She was then prescribed alendronate (10 mg/die), a third generation aminobisphosphonate and a calcium supplement of 1 g/die till the next check-up. The blood tests to assess bone turn-over, performed during her stay in hospital, did not reveal any anomaly, although they were limited to total calcium and alkaline phosphatase. Six months later, on a further admittance for CT exam of the suspected pulmonary lesion, a new DEXA was performed (BMD = 297 mg/cm²) which revealed a 2% increase in bone density.

The treatment with alendronate and calcium supplement was nonetheless continued to verify its efficacy after one year. At the third check-up, a year after the first, there was a further 5.8% improvement in bone mass density compared to the previous exam, with a BMD of 315 mg/cm² and a T score of -1.70. Finally, a bone densitometry performed after another year of treatment revealed a BMD of 336 mg/cm² and a T score of -1.13. A fter two years of treatment with alendronate and the calcium supplement, in addition to the substitutive estroprogestin treatment, the patient had recovered about 6% of bone mass to reach near normal BMD values (Table II).

**Discussion**

Examination of the clinical case described led to the following consideration: alendronate at a dosage of 10 mg per day, administered to an individual suffering from secondary osteoporosis and that had been undergoing substitutive therapy with estrogen for 16 years, considerably enhanced the action of the latter in recovering bone mass. How did this enhancement occur and how was the osteopenic action of L-thyroxine...
overcome? The answer may lie in examining the individual mechanisms of action of estrogens, bisphosphonates and L-thyroxine on the bone metabolism.

- Estrogens have a direct action on the bone due to the presence of specific osteoblastic receptors (that are stimulated), and osteoclastic receptors (with an inhibiting action)\(^{11}\). Their action is then modulated by cytokinin synthesis and growth factors (IL-1, IL-6, IL-2, PG, TNF\(\alpha\)), the production and/or action of which would be altered under the conditions of estrogen deficiency thus favouring the osteoclast formation\(^{12,13}\). The inhibiting action of the estrogens is particularly important on the synthesis of IL-6, a powerful osteoclastogenesis inhibitor, that in menopause is heightened\(^{14}\).

Moreover, a potential role of estrogens in HGH regulation and production was hypothesized\(^{15}\).

Their action on calcium homeostasis should be remembered, in that they stimulate calcitonin secretion, thus causing a reduction in calcium blood levels and consequently PTH and vitamin D3 activation; finally, they increase intestinal calcium absorption. In menopause their deficiency would increase bone tissue sensitivity to PTH, and CT deficiency increases resorption\(^{16}\).

- Bisphosphonates (Bps), owing to their molecular structure, are highly selective in terms of bone tissue; in conditions of greater turn-over they are freed in Howship’s lacunas beneath the surface of the osteoclast and reduce the activity of the protonic pumps. The final result will be a slowing down of the osteoclast lytic activity and formation of fractures that are less deep\(^{17}\).

The Bps would also seem to modify the osteoclast morphology making it functionally less active.

Some theories suggest that in the presence of BPS the osteoclasts diminish in number and become less involved. Moreover, they act indirectly on osteoclast activation by inhibiting osteoblast production of osteoclast activating substances (cytokines)\(^{18,19}\).

According to recent studies Bps penetrate the osteoclast, killing it by apoptosis after deactivating the BCL2 protein\(^{20}\).

The Bps reduce activation of new Bone Multicellular Units (BMU), but do not affect osteoblastic neoformative activity in BMUs that are already active.

It is well known that substitutive or suppressive therapy with thyroid hormones causes a significant imbalance between bone formation and resorption activity, privileging the latter\(^{21}\).

They have a direct affect on bone tissue, particularly cortical, but also trabecular, specifically on the osteoclast resorption phase, by increasing the active BMU\(^{22}\).

The T3 also acts on the osteoblast nuclear receptors (TR alpha 1, alpha 2, beta), and on mRNA with an inhibiting effect on cell replication and protein synthesis (dose-dependant effect)\(^{23}\).

They promote the release of osteoclast activating substances, such as lymphokines (IL-1), and bone resorption stimulants (PGF\(_1\) and PGF\(_2\)). Moreover they increase bone cell sensitivity to PTH.

Table II. BMD variations.

<table>
<thead>
<tr>
<th></th>
<th>TIME 0</th>
<th>TIME 6</th>
<th>TIME 12</th>
<th>TIME 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDBMD mg/cm(^2)</td>
<td>289</td>
<td>297</td>
<td>315</td>
<td>336</td>
</tr>
<tr>
<td>radius</td>
<td>Tscore-2.4</td>
<td>Tscore-2.3</td>
<td>Tscore-1.7</td>
<td>Tscore-1.1</td>
</tr>
<tr>
<td></td>
<td>+ 3%</td>
<td>+ 5.8%</td>
<td>+ 6.7%</td>
<td></td>
</tr>
<tr>
<td>MDBMD mg/cm(^2)</td>
<td>530</td>
<td>536</td>
<td>540</td>
<td>544</td>
</tr>
<tr>
<td>radius</td>
<td>Tscore-2.3</td>
<td>Tscore-2.1</td>
<td>Tscore-1.9</td>
<td>Tscore-1.8</td>
</tr>
<tr>
<td></td>
<td>+ 1.13%</td>
<td>+ 1.88%</td>
<td>+ 2.6%</td>
<td></td>
</tr>
<tr>
<td>BMD of the spine</td>
<td>640</td>
<td>660</td>
<td>670</td>
<td>700</td>
</tr>
<tr>
<td>Tscore-2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ 3.12%</td>
<td>+ 4.7%</td>
<td>+ 6.25%</td>
<td></td>
</tr>
</tbody>
</table>

UDBMD = ultra distal bone mineral density of the radius; MDBMD = medio distal bone mineral density of the radius.
It could be hypothesized that some sort of combined synergism may take place between the estrogen action and the alendronate action: the former would act by slowing down the early phase of bone deconstruction, blocking osteoclastogenesis through the mediated IL-6 mechanism.

The alendronate would act in the later stages of bone deconstruction by antagonising the direct effects of osteoclasts inside the BMU activated by blockage of the protonic pumps.

In our clinical case estrogen alone was not effective.

Further confirmation was provided by our patient’s serum level of estradiol (Table I). Estradiol blood levels capable of impeding bone tissue loss must be greater than 40-60 pg/ml.

It must be remembered that our patient was also being administered L-thyroxine which could have led to the failure of the estrogen treatment.

In conclusion there is no doubt that substitutive estrogen therapy represents the “gold standard” as the pharmacological approach to patients in physiological, surgical or early postmenopause, where no contraindications exist, a valid alternative or highly effective addition could be alendronate. In the specific clinical case described, where our patient is obliged to take l-thyroxine for the rest of her life, the significant recovery of bone mass obtained by the estrogen-alendronate association over the two years, we hope the true benefit, consisting in the absence of fractures, can be maintained into the future.

Various trials have demonstrated that 7% recovery of bone mass reduces the risk of fractures by 50%.

In the end as reported in a recent work of the A Lendronate/E strogen Study G roup the association A lendronate – E strogen is a lot useful in the treatment of the post-menopausal osteoporosis and our case is to assimilate to this type of osteoporosis.

References


24) CASTRO JH, GENUTH SM, KLEIN RL. Comparative response to parathyroid hormone in hyperthyroidism and hypothyroidism. Metabolism 1975; 24: 839-844.


