TAKE CARE OF YOUR BONES!

Bone health in women in therapy with aromatase inhibitors

edited by

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Introduction:

Osteoporosis is a disease characterized by a reduction in bone mass and an alteration of the structure (micro architecture) of the bone tissue which makes the skeleton more fragile and therefore at greater risk of fractures (spontaneous or from minor trauma). The sites at greatest risk of fracture are the vertebrae, especially the dorsal-lumbar ones, the femur and the wrist and more rarely the humerus, the pelvis, the ankle and the foot. In Italy about 5 million people are affected by this disease and more than 80% are postmenopausal women. Osteoporosis is a silent disease as the first sign is fracture. Fractures of the long bones (femur, radius, metatarsal) are always associated with intense pain while those of the vertebrae are often asymptomatic and can sometimes present with intense initial pain which then tends to become chronic. The vertebral fracture determines an accentuation of the dorsal kyphosis and the reduction in height. Osteoporosis can be classified into primary or secondary.

Primary osteoporosis is linked to a natural reduction of bone mass and is classified in: **post menopausal** if it is caused and sustained by the reduction of estrogens that characterizes this phase of a woman's life; **senile** if linked to aging.

As regards **primary post menopausal osteoporosis**, it is linked to a progressive reduction of estrogens, key hormones that regulate the function of the sexual apparatus in the fertile period of the woman, but which are fundamental for the growth and harmonious development of the skeleton and for the acquisition and maintenance of adequate bone mass. The loss of bone mass that occurs during the post menopausal period over the years is very variable (20-30%) and the risk of developing osteoporosis or not will depend on different factors: the initial bone mass (i.e. the one acquired in the skeletal maturation phase, that has its peak between 16 and 18 years in females), the rapidity-reduction of estrogen level in the menopausal period, vitamin D levels, the introduction of calcium in the diet and physical activity. In fact, the faster the estrogen reduction is, the greater the decline of quantity and quality of the bone is.

The **secondary osteoporosis** is linked to other diseases (endocrine, gastrointestinal, blood diseases) or comes from the use of particular drugs.

Finally, cigarette smoking, alcohol, coffee, thinness, a calcium deficient diet, a sedentary lifestyle, a late menarche and an early menopause are also factors favoring osteoporosis.

Osteoporosis due to aromatase inhibitors

In regard to osteoporosis secondary to drugs, among these we find the aromatase inhibitors (letrozole, anastrozole, exemestane) which have now become the key therapy treatment of endocrine-responsive breast tumors in postmenopausal women, tumors that represent about 70% of those diagnosed after menopause.

The endocrine-responsive tumors are stimulated in their growth by estrogens which are also present in postmenopausal women. In fact, once the estrogenic production of ovaries in the female body has stopped, even in menopause these hormones are produced by the adrenal gland and peripheral fat through an androgens-transformation process, thanks to the activity of an enzyme called aromatase.

Therefore in postmenopausal women who develop hormone-responsive breast cancer it will be necessary to turn off this production through the inhibition of this enzyme. It is intuitive to understand how, the complete elimination of estrogen production (supermenopause) determined by the aromatase inhibitors, which allows to obtain the protective effect on the tumor, determines a further decay of the quality of bone favoring osteoporosis. Considering the rapid estrogenic zeroing induced by aromatase inhibitors, the risk of developing an osteoporotic fracture increases already in the first 12 months of therapy. The risk then continues to increase over time and the longer the treatment period is, the greater the risk of fracture becomes. The standard therapy for the treatment of endocrine-responsive tumors is 5 years but can be extended to 10 years in women at increased risk of recurrence. Obviously, the starting skeletal situation is important: if before starting aromatase inhibitor therapy there has already been a fracture or if you are already aware of a reduced bone mass, the risk of fracture increases further. Finally, it should also be noted that fracture related to aromatase inhibitor therapy occur in the presence of an almost normal or only modestly reduced (MOC/DEXA) densitometric examination. As fractures often occur as we have said in an asymptomatic way and the bone mass is not always significantly altered, to monitor the situation it is useful to measure the patient's height (the loss of 1-2 cm in height is already a valid suspicion of spine damage). Furthermore specific blood tests for bone metabolism (calcium, vitamin D, parathyroid hormone) should be carried out.

What should be done?

Therapy with aromatase inhibitors represents today the first choice of treatment for postmenopausal hormone-responsive breast cancer and is an integral part of daily life of over 250.000 women every year. Since however we know that this therapy has a negative effect on the skeleton, it is good to start in menopausal women, simultaneously with adjuvant (preventive) breast cancer therapy with aromatase inhibitors, a treatment that protects bone health. This treatment to prevent bone damage is even more necessary the longer the therapy with aromatase inhibitors has to be prolonged.

Since the skeletal damage caused by aromatase inhibitors is precocious and subtle, as it is often asymptomatic and not measurable, AIFA (Italian Medicines Agency) has made antiresorptive treatment (drugs that inhibit bone reabsorption) reimbursable since 2015 for women on adjuvant treatment. Recently it has been made possible to start these drugs in primary prevention, i.e. at the same time of when you start treatment with inhibitors before the occurrence of an adverse event (decreased bone mass or fracture).

How to prevent bone fragility?

1. Ensuring the normalization of vitamin D levels is essential for bone health but not effective on its own to minimize the risk of reduced bone mass or fracture.

2. Use antiresorptive drugs on advice of the oncologist for the entire period of intake of the aromatase inhibitor. To make the treatment effective it is necessary to strictly adhere to the indications provided by the doctor.

3. Evaluate bone health at the end of treatment with aromatase inhibitors to see whether to interrupt antiresorptive drugs or go on with therapy.

What drugs can we rely on?

Bisphosphonates: these drugs are able to fix the bone surfaces electively, stopping the degradation activity of the bone with a consequent increase in skeletal density. They are quite well tolerated especially in the weekly formulation even if they can cause gastric disturbances. For this reason they should be taken on an empty stomach in the morning and it is recommended not to lie down or bend over but to keep the torso erect for about half an hour. Very high doses, which are not those used for osteoporosis, can cause mandibular osteonecrosis (ONJ) in 1% of patients, which consists of osteomyelitis (bone infection caused by bacteria) affecting the jaw and which is promoted by dental procedures such as extractions or implants. At the doses used for osteoporosis the risk for therapies of less than 3 years and without associated risk factors (smoking, diabetes, use of immunosuppressants, cortisone and alcohol) is minimal and therefore does not require particular precautions. In patients who need to follow a treatment for more than 3 years or with associated risk factors, it is advisable to have adequate oral hygiene with regular dental check-ups (at least every 6 months). In case it is necessary to perform dental extractions or other interventions, it is essential to discuss with the dentist and the oncologist whether to suspend the drug.

Most bisphosphonates are to be taken orally (tablets) while zoledronic acid is in intravenous formulation.

Denosumab: it is a monoclonal antibody capable to neutralize a cytokine called RANKL which controls the activity of the osteoclasts, the cells that determine bone degradation. In every aspect it works like bisphosphonates causing an anti-resorbing effect, however with some peculiarities: 1) the anti-resorbing effect stops at the interruption of the drug; 2) greater effect than classic bisphosphonates on bone density; 3) chronic therapy leads to a constant increase in bone activity unlike classic bisphosphonates where after 3 years a stabilization of density is obtained. It is a drug that is injected under the skin every 6 months and as for the classic bisphosphonates is related to a rare risk of mandibular osteonecrosis. Therefore, the same precautions in oral care apply as described for bisphosphonates.

What should I do when starting and during treatment with bisphosphonates or Denosumab?

- Since prevention is better than cure, before starting a treatment with bisphosphonates or Denosumab it is always useful to perform a basic dental evaluation, advising the dentist of the start of treatment. In case surgical treatments of the oral cavity were necessary, it is useful to perform them before starting therapy with anti-resorbitives. During therapy it is necessary to maintain an adequate oral hygiene by carrying out regular dental check-ups.
- Take vitamin D regularly according to doctor's instructions throughout all treatment period.
- Take the required daily amount of calcium from your diet.

Beyond therapies

In addition to specific therapies for treatment or prevention of osteoporosis related to the use of aromatase inhibitors, our lifestyle is also fundamental.

Therefore it is necessary to:

1. Avoid bad habits such as alcohol and smoking
2. Take an adequate amount of calcium and vitamin D from your diet
3. Do moderate but constant physical exercise

Avoid bad habits

Smoking is a risk factor for osteoporosis. In fact, smokers and former smokers have an increased risk of fracture compared to non-smokers. Smoking is associated with several other risk factors for osteoporosis including premature menopause and excessive thinness.

Alcohol is also a predisposing factor for osteoporosis since its excessive and prolonged use determines an interference in the synthesis process of the bone tissue, a modification of the cellular and hormonal micro environment of the tissue. It also increases the risk of falling and is associated with an insufficient intake of vitamin D and calcium.

It is also reported that extreme thinness is associated with increased loss of bone mass. People with a BMI of 20kg/m2 have a doubled risk of fracture compared to normal weight individuals.

Take an adequate amount of calcium and vitamin D from your diet

A balanced diet that includes a correct intake of calcium, vitamin D, proteins and other important nutrients for bones is an essential factor for the health of the skeleton.

On average, adults between the ages of 19 and 50 needs 1 gram a day of calcium. This level increases to 1,2 grams per day for women aged 51 to 70 and to 1,3 grams per day for pregnant ones. Surprisingly, most people do not get the right amount of calcium through their diet.

Foods rich in calcium are milk and its derivatives, but contrary to popular belief, they are not the only foods that contain high amounts of calcium. The main sources of calcium are:

1. **Yogurt and cheese** - by far the richest foods in calcium, include milk, yogurt and cheeses. Among the "made in Italy " products, Parmesan cheese contains a very high percentage of calcium (every 28 grams contains about 33% of the amount of calcium to be consumed in a day). In general, aged cheeses are lactose-free foods with higher amounts of calcium than fresh ones and can be safely taken by those who are intolerant to this sugar. A cup of yogurt, on the other hand, contains 30% of the daily calcium requirement and is a very important product for your health thanks to the presence of probiotes and vitamins B2 and B12.

2. **Green leafy plant foods** - among the richest foods in calcium we mention broccoli, spinach and cabbage. A cup of boiled green cabbage contains a quarter of the amount of calcium needed in a day.

3. **Fish** - anchovies and salmon are foods rich in calcium. 92 grams of anchovies contain 35% of the daily calcium requirement. If you fear the presence of mercury in fish, both anchovies and salmon have a high amount of selenium, which neutralizes the toxic effects of mercury.

4. **Sesame and flax seeds** - sesame seeds bring a conspicuous amount of calcium. A spoon of sesame seeds (ca. 15 grams) contains 126 mg of calcium, while a spoon of flax seeds holds 38 mg. Both products are great to enrich bread, salads and soups.

5. **Beans and lentils** - as well as being a source of calcium (ca. 24% of daily need), beans and lentils also contain a high concentration of fibers, proteins, iron, zinc, folate, magnesium and potassium.

6. **Almonds** - almonds contain not only calcium but also magnesium and iron. Their fat and protein content affects heart health by lowering the level of harmful cholesterol in the blood.

7. **Soy** - soy is a highly digestible legume with many properties: it contains calcium, magnesium, iron, vitamins and many proteins, non-harmful fats, lecithin and glucides. From soy milk comes Tofu which contains 14% of the daily amount of calcium necessary for the body.

8. **Rhubarb** - rhubarb is one of the calcium-rich plant foods and contains a lot of fiber.

9. **Quinoa** - quinoa, like spinach and beetroot, is a herbaceous plant of the Chenopodiaceae family. It contains between 60 and 100 mg of calcium every 100 grams and has a high content of potassium, zinc and proteins.

10. **Dried figs** - dried figs are among the foods rich in calcium and lactose. Eight dried figs contain ca. the same amount of calcium present in a glass of milk.

It is very important to vary calcium intake with food also because for a correct, healthy diet it is better to reduce milk, dairy products and similar.

In addition to food, there are some **mineral waters** which have a high calcium content.

Vitamin D

The presence of vitamin D is necessary since it helps the absorption of calcium contained in food, ensuring adequate bone protection and the good functioning of the muscles, improving therefore their tone and strength. Vitamin D is mainly formed by the exposure of the skin to the sun. In our latitudes this is possible only in summer. With aging however the skin is less effective in producing vitamin D (older people produce only a tenth compared to younger ones).

Foods rich in vitamin D are salmon, cod liver oil, mackerel, tuna, herring, sardines, eggs. On average the recommended intake of vitamin D is 400-800 units per day.

In deficiency conditions, a supplement must obviously be provided with a dosage related to the deficiency status of the individual. For example, high dosages of vitamin D are necessary in case of reduced chronic or forced sun exposure, malabsorption or intake of drugs such as cortisone or anticonvulsants.

Exercise

After menopause, physical exercise becomes essential for maintaining bone mass and muscle strength. In addition to maintaining bone mass, the main goal of exercise is to increase muscle mass to improve its function, balance and strength. Reduced muscle tone and poor balance can promote falls and fractures. The positive effect of exercise on the bone depends on both the type and intensity of physical activity. Exercise has the effect of promoting a modest improvement in bone mineral density of approx. 1-2%. Exercise programs should be chosen according to the needs and abilities of each individual, especially in the presence of osteoporosis. Sedentary life instead determines a progressive impoverishment of the skeletal structure. Moreover, regular physical activity also allows an improvement in the prognosis of breast cancer and also controls the clinical symptoms (joint pains) often correlated with the use of aromatase inhibitors and menopause. At least 30-40 minutes a day of moderate anti-gravity physical exercise is recommended such as walking or dancing. Age-appropriate aerobic and resistance exercises may also be helpful. For those who cannot do physical activity due to other co-pathologies it would be useful to perform postural gymnastics. In presence of osteoporosis it is good to avoid overloading the spine, twisting and bending movements of the lumbar spine. Practicing regular physical exercise also reduces the risk of accidental falls, for which it is also necessary to carry out the right prevention by using adequate footwear, by the elimination of domestic obstacles (carpets, slippery surfaces) and a correct lighting of domestic environments.

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