To prevent the osteoporosis playing in advance

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Summary

There are several possibilities for the prevention of primary, secondary and tertiary osteoporosis but till now they have not been promoted enough and bone fragility is thought about only after the onset of a fracture (tertiary prevention). By recent studies and discoveries it is becoming increasingly clear that there is a relationship between growth and development in early childhood and bone health in old age. Suboptimal bone development leads to a reduction in peak bone mass, and a higher risk of osteoporotic fracture later in life. Preventative strategies against osteoporosis can be aimed at either optimizing the peak bone mass obtained, or reducing the rate of bone loss. Optimization of peak bone mass may be more amenable to public health strategies. Technological advances and our knowledge of osteoporosis have increased in the last decade and so tertiary prevention should be considered a failure in the field of public health. If we want to make advances in the osteoporotic field, we must start in childhood, before the bone mass peak is reached and the gold-standard is starting with prevention as soon as possible, also during fetal development.

KEY WORDS: osteoporosis; prevention; childhood; peak bone mass.

Osteoporosis is the most common bone disorder in Western populations and an important public health issue due to the potentially devastating consequences of fragility fractures. Osteoporotic fractures have a major impact upon health, both in terms of acute and long term disability and economic cost. Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility (1). Many studies have shown that fractures are a common problem in childhood, with around one-third of boys and girls sustaining at least one fracture before 17 years of age. Fractures are more common among boys than girls, with peak incidences at 14 and 11 years of age, respectively. After this childhood peak, incidence rates were only surpassed later in life at 85 years of age among women and never among men (2, 3). The progression of osteoporosis and fragility fractures has certainly been advanced by the enhancement in life expectancy, and the increased survival of children with chronic medical conditions predisposed to bone loss, as well as changed eating habits. There are several possibilities for the prevention of primary, secondary and tertiary osteoporosis but till now they have not been promoted enough and bone fragility is thought about only after the onset of a fracture (tertiary prevention).

In regard to primary prevention, we know that genetics plays an important role, but they are not the only factor which determines bone mass. The progressive increasing of bone mass throughout childhood and adolescence reaches a peak in early adulthood. It then declines in older age, through loss of bone tissue (thinning of the trabeculae and cortex), with an accelerated rate of decline at menopause. Osteoporosis is a major cause of morbidity and mortality through its association with fragility fractures. Although this crucial characteristic is partly inherited, currently identified genetic markers only explain a small amount of the variation in individual peak bone mass and fracture risk (4).

It is becoming increasingly clear that there is a relationship between growth and development in early childhood and bone health in old age. In fact, suboptimal bone development leads to a reduction in peak bone mass, and a higher risk of osteoporotic fracture later in life. Preventative strategies against osteoporosis can be aimed at either optimizing the peak bone mass obtained, or reducing the rate of bone loss. Optimization of peak bone mass may be more amenable to public health strategies (5). As mentioned before, evidence is accruing that environmental factors may act early in development (in utero and early postnatal life), interacting with the genome to produce a persisting influence on postnatal skeletal development and it has now been shown that growth in utero and early childhood is associated with actual risk of fracture (6). Fetal development and early childhood may be a critical period for the development and/or programming of metabolic systems, including the skeleton.

There is increasing human data from cohort studies on the association between early childhood nutrition and bone development in children. In particular, there is evidence which suggests that subclinical vitamin D deficiency does affect bone acquisition, potentially beginning in utero and extending into adolescence (7). Calcium and vitamin D, key nutrients in the process of bone formation, have been studied in children involved in a nutrition in pregnancy study. It has been shown that bone mass in childhood was positively associated with a corrected calcium level in the umbilical cord of the child at birth. A lower concentration of serum 25(OH) vitamin D in mothers during late pregnancy was also associated with reduced whole-body and lumbar spine BMC (Bone
Mineral content) in 9-year-old children. Maternal vitamin D status was significantly associated statistically with childhood bone area, and areal BMD (Bone Mineral Density). Estimated exposure to ultraviolet B radiation during late pregnancy and the maternal use of vitamin D supplements both predicted maternal 25(OH) vitamin D concentration, and childhood bone mass (8, 9).

Future understanding of the mechanisms by which maternal diet and behavior influence offspring skeletal development may suggest focused interventions to improve skeletal health throughout the course of life, and reduce the burden of osteoporotic fracture in future generations. Scientific research also documents that later pubertal timing is associated with increased incidence of fracture during childhood and adolescence (10). Other studies have confirmed that to reach an adequate bone peak mass, physical activity plays an important role; in a recent population-based study, a moderately intense 4-year exercise program in 7- to 9-year-old children increased bone mass and size without affecting fracture risk (11).

A thorough patient history is important to gauge predisposition and provide secondary prevention of osteoporosis with an emphasis on bone frailty, lifestyle, eating habits, risk factors with laboratory tests and imaging studies. There are several technologies to measure BMD and they can be used also in children, therefore we can study the progressive increasing of bone mass throughout childhood and adolescence. In recent years, different methods have been developed to study bone mineral density:

- Ultrasound devices are available for the Italian population with reference curves that consider the height, age and pubertal stage but should not be used in the follow-up of therapy because they show very slow changes in adjustable relation to the need of therapeutic control.
- The pQCT allows for volumetric assessments of BMD, especially in the forearm but applications have been reduced because of high costs and high radiation doses.
- The DXA assessment is the gold standard and guidelines are published, as indicated by the International Society for Clinical Densitometry (ISCD), for the execution of such an investigation and the evaluation of data obtained in children. In view of the evolution of diagnostic bone densitometry and determination of appropriate reference curves in the period of skeletal growth, the ISCD has recommended since 2007 to separate adults from the young (5 to 19 years) in densitometric assessment (12). The diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone. It requires the presence of a clinically significant fracture history due to low trauma. Other markers of skeletal health should be evaluated, such as bone age and Tanner’s pubertal stage.

Concurring with the ISCD, we can make a diagnosis of osteoporosis in childhood when there is an areal bone mineral density with Z-score (the age-adjusted mean value) below more than 2.0 Standard Deviations (SD), with a significant clinical fracture history of the following:

- Long bone fracture of the lower extremities
- Vertebral compression fracture
- Two or more fractures of long bones of the upper extremities

Densitometry should be performed in all young subjects with:

- Primitive bone disease or potential metabolic bone disease (Table 1)
- Thalassemia major from early childhood and or fractures at age 10
- Two or more fractures of long bones of the upper extremities
- More fractures of the lower extremities
- Vertebral compression fracture
- Chronic immobilization
- Before starting a bone-specific therapy

Following this approach, clinical practice requires the exclusion of secondary causes of osteoporosis (Table 1). Later in life, secondary prevention requires attention in all patients over 65 years of age. Before this period we must prescribe a DXA in presence of a fragility fracture, risk factors such as early menopause (<45 years), slimness (<57kg), tabagism, and medications or diseases that impact bone metabolism increasing fracture risk (13).

Technological advances and our knowledge of osteoporosis have increased in the last decade and so tertiary prevention should be considered a failure in the field of public health. If we want to make advances in the osteoporotic field, it is already too late to start treatment in adults, we must start in childhood, before the bone mass peak is reached. Diet, a modifiable osteoporosis risk factor, plays an important role in the acquisition and maintenance of bone mass. The influence of diet on bones begins in childhood and maternal diet can influence bone mass in the offspring. A good, general nutritional diet, with adequate dietary protein, calcium, vitamin D, fruits, and vegetables, has a positive influence on bone health, while a high caloric diet and heavy alcohol consumption have been associated with lower bone mass and higher rates of fracture (14).

A proper prevention plan can be aimed at either optimizing the peak bone mass obtained, or reducing the rate of bone loss. Optimization of peak bone mass may be more amenable to public health strategies, and it should be implemented in early childhood, starting from the intrauterine period and maintained in childhood and adolescence until skeletal maturity. We hope in the future general practitioners and public engagement will promote more awareness of how the osteoporosis problem starts early in life by increasing the population’s knowledge with public information and awareness campaigns.

### Table 1 - Etiology of osteoporosis in children.

<table>
<thead>
<tr>
<th>Primary bone disorders</th>
<th>Chronic inflammatory diseases</th>
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<tbody>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Chronic inflammatory arthritis</td>
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<tr>
<td>Hypothyroidism</td>
<td>Dermatomyositis</td>
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<tr>
<td>Childhood rickets</td>
<td>Rheumatoid arthritis</td>
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<td>Marfan syndrome</td>
<td>Inflammatory-based disease</td>
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<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Hypertrophic osteosis</td>
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<tr>
<td>Infantile ossification</td>
<td>Immobility or decreased activity</td>
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<tr>
<td>Osteogenesis imperfecta</td>
<td>Post-trauma</td>
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<tr>
<td>Congenital bone deformity</td>
<td>Cerebral palsy</td>
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<tr>
<td>Cushing syndrome</td>
<td>Spinal muscular atrophy, Muscle atrophy</td>
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<tr>
<td>Marfan syndrome</td>
<td>Endocrine disorders</td>
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<td>Hypertension</td>
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<td>Marfan syndrome</td>
<td>Cushing syndrome</td>
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<td>Marfan syndrome</td>
<td>Other causes of osteoporosis</td>
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### References

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