Prevention and treatment of osteoporosis in women: an update

Anna Daroszewska

Abstract

Osteoporosis is the most common metabolic bone disease and its prevalence is expected to increase in the aging population. Peak bone mass, a key predictor of osteoporosis and fractures, is to a degree determined *in utero*. Interventions at early stages of foetal development by optimising the health and well-being of the mother and later in childhood, have been shown to increase bone mass. Treatment of postmenopausal osteoporosis is aimed at reducing fracture risk and bisphosphonates remain the mainstay of anti-resorptive therapy. Denosumab, a monoclonal antibody against RANKL, is an alternative for patients intolerant of or with contraindications to bisphosphonates. Anti-fracture efficacy of anti-resorptives by far outweighs the small risk of atypical fractures associated with long-term use. Anabolic treatment with teriparatide, is reserved for severe osteoporosis. Novel agents: monoclonal anti-sclerostin antibody, romosozumab and specific cathepsin-K inhibitor, odanacatib are in clinical trials and expected to enter clinical use in the near future.

Keywords osteoporosis; postmenopausal; prevention; review; treatment

Introduction

Osteoporosis is characterised by low bone mass and deterioration in bone architecture which predispose to fragility fractures. Approximately 2 million women in the UK and 200 million women worldwide are affected and the prevalence is expected to rise as the population ages. The annual cost of osteoporotic fractures is over £2 billion and predicted to treble within the next 25 years. Approximately 80% of the cost relates to hip fractures, which carry the highest morbidity and mortality. A 50-year-old woman has an approximately 50% lifetime risk of suffering an osteoporotic fracture and pre-existing fractures increase the risk of subsequent fractures.

The diagnosis of osteoporosis is usually made on the basis of the bone mineral density (BMD) of the lumbar spine and hip measured by dual-emission X-ray absorptiometry (DEXA). In a peri- or post-menopausal woman a T-score ≤ -2.5 (at least 2.5 standard deviations below the average BMD of a young woman) defines osteoporosis according to the World Health Organisation (WHO). A T-score between -1 and -2.5 signifies osteopenia. In young premenopausal women with a T-score ≤ -2.5 (unless still growing and have not achieved peak bone mass) the diagnosis of osteoporosis can be made in the presence of a chronic disease known to affect bone metabolism (inflammatory, metabolic or gonadal insufficiency). Otherwise the BMD is assessed by Z-scores (age-correlated) and Z-scores ≤ -2 and > -2 define BMD below and within the expected range for age respectively.

Although BMD is the main determinant of bone strength, other skeletal and non-skeletal factors contribute to the overall fracture risk and a number of these are included in the Fracture Risk Assessment Tool (FRAX), commonly used in clinical practice. Typical assessments and procedures necessary in investigating suspected osteoporosis are listed in Box 1.

The aim of treatment of osteoporosis is to reduce moderate and high fracture risk. FRAX (www.shef.ac.uk/FRAX) is a computer-based algorithm, which estimates the 10-year fracture risk probability for a major osteoporotic (hip, spine, humerus and wrist) and hip fracture. FRAX takes into account several risk factors for fragility fractures: age, low BMI, prior fragility fractures, parental history of hip fracture, smoking, daily alcohol intake of over 3 units, use of oral glucocorticoids, rheumatoid arthritis and other causes of secondary osteoporosis (type 1 diabetes mellitus, osteogenesis imperfecta, untreated hyperthyroidism, hypogonadism and/or early menopause [<45 years], chronic malnutrition, malabsorption and chronic liver disease). FRAX is linked to guidelines of the National Osteoporosis Guideline Group (NOGG), which display a treatment threshold and aid management decisions.

A number of non-pharmacological and pharmacological interventions are available and being developed and their use is based on the understanding of the pathophysiology of bone homeostasis. Bone is a dynamic tissue, which undergoes renewal in the process of bone remodelling, key for bone repair. The bone remodelling cycle is initiated by bone-resorbing cells, osteoclasts and completed by bone-forming cells, osteoblasts (which by the end of the process are embedded in bone matrix and become

Investigations and procedures in the assessment of osteoporosis

- Careful history (including estimation of dietary calcium intake)
- Clinical examination
- Laboratory blood tests: full blood count, erythrocyte sedimentation rate, or plasma viscosity, or C-reactive protein, serum calcium, phosphate, alkaline phosphatase, creatinine, liver function tests, thyroid function tests, protein immunoelectrophoresis, 25(OH)Vitamin D, endomysial and/or tissue transglutaminase (TTG) antibodies, bone turnover markers (if available)
- Laboratory urine tests: Bence-Jones protein, 24 hour urine collection for calcium excretion (if indicated, eg in malabsorption)
- Bone densitometry (with lateral vertebral fracture assessment, VFA, if available)
- Lateral radiographs of thoracic and lumbar spine (if indicated, e.g. VFA not available)
- Calculation of fracture risk probability (e.g. Fracture Risk Assessment Tool, FRAX)

Box 1

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osteocytes). Osteoclasts secrete hydrochloric acid and cathepsin-K, which dissolve bone mineral and collagen respectively.

The C-terminal cross-linking telopeptide of type I collagen (CTX) is a breakdown product of type-1 collagen (the most abundant collagen in bone), detectable in the serum and urine and serves as a bone resorption marker. A common bone formation marker is the procollagen type 1 N-terminal propeptide (P1NP).

At a molecular level, osteoclastogenesis is initiated by stimulation of the receptor activator of nuclear factor-κ B (RANK), expressed on pre-osteoclasts, with its ligand (RANKL), expressed primarily by osteoblasts and osteocytes. An endogenous soluble RANKL-decoy receptor, osteoprotegerin (OPG) inhibits osteoclastogenesis by blocking RANKL. Osteoblast differentiation and bone formation is triggered by the activation of the Wnt-signalling pathway, which is controlled by two endogenous Wnt-antagonists: sclerostin expressed by osteocytes and dickkopf-1 (Dkk-1) mainly expressed by osteocytes and osteoblasts.

Epigenetic factors influence bone remodelling and micro RNAs (miRNAs): miR-21, miR-23a, miR-24, miR-100 and miR-125b are elevated in patients with osteoporotic fractures, thus being attractive candidates to become disease-specific biomarkers and predictors of fracture risk in the future.

Non-pharmacological management strategies

Peak bone mass (PBM), achieved by age 30, is a key predictor of osteoporotic fractures at older age and evidence suggests that PBM is to a degree determined *in utero*. Intra-uterine environmental factors (maternal nutritional state, vitamin D status, stress) affect epigenetic mechanisms underlying developmental plasticity including the formation of the foetal skeleton.

Mineralisation of the foetal skeleton is mostly achieved in the third trimester, which is reflected by increased maternal calcium intestinal absorption. Thus low maternal calcium intake and/or suboptimal vitamin D status may be a risk for low bone mass in neonates and later in childhood. A longitudinal study of nearly 200 children showed that low maternal 25(OH)D during late pregnancy was associated with reduced whole-body and lumbar spine bone mineral content (BMC) in their children at the age of 9. Other risk factors included low maternal height and preconception weight, low fat stores, smoking and lower social class.

Accumulation of bone mineral during childhood and adolescence is governed by heredity and modifiable factors including diet, smoking, endocrine status and physical exercise. A recent prospective controlled study of over 2500 Swedish children aged 6 to 9 demonstrated that 40 minutes of daily physical activity, introduced as part of routine play (running and jumping) at school over 6 years significantly improved bone mass and bone size in girls without affecting the fracture risk.

As low rate age-related bone loss may already begin after the age of 30 in parallel to the decline in muscle mass, a healthy lifestyle (regular weight bearing exercise, healthy diet) is important. Recent evidence suggests that soluble dietary fibre significantly changes the gut microbiome and improves intestinal calcium absorption. Low BMI is a known risk factor for osteoporosis, however obesity is associated with a higher rate of vitamin D deficiency and may also predispose to fragility fractures. Thus maintenance of an ideal BMI should be encouraged.

In the elderly, falls are a significant risk factor for fragility fractures and single- and multifactorial fall prevention strategies reduce this risk. These include individual assessment and modification of risk factors for falling such as poor mobility, dizziness-inducing medication, postural hypotension, vision impairment, foot problems, inadequate footwear, tripping hazards and the fear of falling. Multi-component exercise programs applied on an individual or group basis (e.g. Tai-Chi) have been shown to reduce the risk of falling.

Calcium and vitamin D

An optimal dietary calcium intake is important for the attainment of PBM and maintenance of optimal BMD. Calcium-rich foods include dairy products, green vegetables and fish. The recommended daily dietary calcium allowance (RDA) for adolescents and women $\leq$50 (including pregnant and breastfeeding) is 1300 mg and 1000 mg with the tolerable upper level (UL) intake of 3000 mg and 2500 mg respectively according to the US Institute of Medicine (IOM). For postmenopausal women calcium RDA and UL are 1200 mg and 2000 mg respectively. In clinic dietary calcium intake is estimated with dietary questionnaires and if low a higher dietary intake or calcium supplementation is recommended.

Vitamin D is essential for maintaining calcium and phosphate homeostasis. The active form of vitamin D increases intestinal calcium and phosphate absorption, osteoclast-mediated bone resorption and renal calcium re-absorption. Low vitamin D causes rickets in children and impairment of bone mineralization or osteomalacia in adults. Vitamin D is synthesised in the skin during exposure to the UVB light, but many factors (higher latitude, overcast sky, air pollution, dark and/or aged skin, clothing, sun-blocks) diminish this process. In the UK between October and April virtually no vitamin D is synthesised in the skin and one relies on vitamin D stores accumulated in summer and dietary intake. The main dietary sources of vitamin D are oily fish, however an average diet alone provides only approximately 10 −20% of vitamin D requirement.

Vitamin D needs two hydroxylation steps to become metabolically active. The first step takes place in the liver, where the 25-hydroxylase converts vitamin D to 25(OH)Vitamin D [25(OH)D], serum concentration of which is used to determine vitamin D status. The second step takes place in the kidneys, where 25(OH)D is converted to $1,25(OH)_2D$ by the 1α-hydroxylase. $1,25(OH)_2D$ is metabolically active and regulates approximately 2000 genes, directly through the nuclear vitamin D receptor (VDR) or indirectly. In the circulation both forms bind to vitamin D binding protein (DBP) and less so to albumin and both are important at different stages of vitamin D metabolism and activity. Black individuals have lower 25(OH)D and DBP (but a similar estimated unbound 25[OH]D) and higher serum calcium and higher BMD then white counterparts.

Opinions differ with regard to the 'normal' concentration of 25(OH)D. The US IOM guidelines based on a population model of vitamin D deficiency prevention for 97.5% of the population propose that 25(OH)D of 50 nmol/Litre (20 ng/mL) is sufficient. However most authorities agree that the optimal 25(OH)D for bone health is $\geq$75 nmol/Litre (30 ng/mL), as at this concentration the parathyroid hormone (PTH) is at its nadir, intestinal