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ESSENTIALS Osteoporosis is characterized by a reduction in bone mass and dis- ruption of bone architecture, resulting in increased bone fragility and fracture risk, with fractures of the distal radius (Colles' fracture), spine, and proximal femur being most characteristic. One in two women and one in five men over the age of 50 years will suffer an osteo- porotic fracture during their remaining lifetime, with massive cost to healthcare services. Pathogenesis—bone mass in later life depends both on (1) peak bone mass achieved in early adulthood—strongly influenced by gen- etic factors, also sex hormone status, nutrition, and physical activity; and (2) rate of age-related bone loss; oestrogen deficiency is a major factor in menopausal bone loss in women. Diagnosis—dual-energy X-ray absorptiometry is the best method for measuring bone mineral density at the spine and hip, with osteoporosis defined as present when the bone mineral density is 2.5 standard deviations or more below normal peak bone mass (T-score ≤ −2.5). Risk assessment—an algorithm (FRAX) to estimate 10-year fracture probability uses (1) clinical risk factors—including age, glucocorticoid therapy, a previous history of fracture, a family history of hip fracture, current smoking, alcohol abuse, and certain diseases associated with osteoporosis (e.g. rheumatoid arthritis); with or without (2) bone mineral density measurements. This enables intervention thresholds to be based on absolute risk rather than on bone mineral density T-scores. Treatment—appropriate levels of exercise should be recommended and smoking and alcohol abuse discouraged. In postmenopausal women with osteoporosis, reductions of around 30–70% in vertebral fracture are seen after three years' treatment with most drug interven- tions, with the current consensus being that this should be continued for a minimum of five years. (1) First-line treatments—for postmenopausal women: these would generally be regarded as alendronate, risedronate, zoledronic acid (all bisphosphonates), denosumab. (2) Second-line treatments—raloxifene (a selective oestrogen- receptor modulator), ibandronate, or strontium ranelate. (3) Other considerations: (a) intravenous zoledronic acid: the treat- ment of choice when

oral medication cannot be given or will not be absorbed; (b) teriparatide: use may be limited to women with severe
vertebral osteoporosis who are intolerant of or unresponsive to other treatments; (c) hormone replacement therapy: an appropriate option in younger postmenopausal women at high risk of fracture; (d) calcium and vitamin D: should be co-prescribed with other treat- ments if there is evidence of inadequate calcium intake or vitamin D
insufficiency; (e) glucocorticoid-induced osteoporosis: primary
prevention with a bisphosphonate is recommended for patients committed to any oral dose of prednisolone for more than three months who are older than 65 years or who have sustained a previous fragility fracture. Other patients taking oral glucocorticoids for over three months should have their bone mineral density meas- ured, and those with a T-score of −1.5 or lower should be considered for treatment. Recent guidelines have placed these considerations into the context of absolute risk assessment. Introduction Osteoporosis is characterized by a reduction in bone mass and dis ruption of bone architecture, resulting in both increased bone fra gility and consequent fracture risk. These fractures, which lead to substantial morbidity and mortality, are widely recognized as a major health problem in the older population, resulting in an es timated annual cost to British health services of £3 billion. One in two women and one in five men over the age of 50 years will suffer a fracture due to osteoporosis during their remaining lifetime. Demographic changes over the next 50 years are predicted to lead to at least a doubling in the number of these fractures, largely as a result of increased longevity. Epidemiology Osteoporotic fractures are termed fragility fractures (defined as occurring after a fall from standing height or less). They may occur at several skeletal sites, but fractures of the distal radius (Colles' fracture), spine, and proximal femur are most characteristic. The incidence of osteoporotic fractures increases markedly with age; in women, the median age for Colles' fractures is 65 years and for 20.4 Osteoporosis Nicholas C. Harvey, Juliet Compston, and Cyrus Cooper

20.4 Osteoporosis 4697 hip fracture, 80 years. The age at which vertebral fracture incidence reaches a peak has been less well defined but is thought in women to be between 65 and 80 years. In men, no age-related increase in forearm fractures is seen but hip fracture incidence rises exponen tially after the age of 75 years. The prevalence of vertebral fractures rises with age in men, although less steeply than in women. Clinical features Colles' fractures typically occur after a fall forwards on to the out stretched hand. They cause considerable inconvenience, usually re quiring four to six weeks in plaster and long-term adverse sequelae are seen in up to one-third of patients. These include pain, sympa thetic algodystrophy, deformity, and functional impairment. Vertebral fractures (Fig. 20.4.1) may occur spontaneously or as a result of normal activities such as lifting, bending, and coughing. A minority of vertebral fractures (possibly around one-third) pre sent with acute and severe pain at the site of the fracture, often ra diating around the thorax or abdomen. The natural history of this pain is variable; in general, there is a tendency for improvement with time, but resolution is often incomplete. Multiple vertebral fractures result in spinal deformity (kyphosis), height loss, and corresponding alterations in body shape with protuberance of the abdomen and loss of normal body contours. These changes are commonly associ ated with loss of self-confidence and self-esteem, difficulty with daily activities, and increased social isolation. The clinical impact of ver tebral fractures is thus substantial, although often underestimated. Of all the osteoporotic fractures, hip fractures cause the greatest morbidity and mortality. They almost always follow a fall, either backwards or to the side, and require admission to hospital and surgical treatment. Because hip fractures characteristically affect frail

older people, postoperative morbidity and mortality are high; at six months after fracture, mortality rates of 12–20% have been reported. Only a minority of sufferers regain their former level of independence following a hip fracture and up to one-third require institutionalized care. Pathogenesis Lifetime changes in bone mass are shown in Fig. 20.4.2. Peak bone mass is attained in the third decade of life and age-related bone loss is believed to start in both men and women around the beginning of the fifth decade; thereafter bone loss continues throughout life. In women, there is an accelerated rate of bone loss around the time of the menopause, the duration of which is poorly characterized but can be 5–10 years. Bone mass in later life thus depends both on the peak bone mass achieved in early adulthood and on the rate of age-related bone loss. Although there is a substantial heritable com ponent to peak bone mass, and several individual genes related to adult bone mineral density have been identified from genome wide association studies, the combined effect of these genes only explains a very small proportion of the overall variation. Additionally, there is much evidence that environmental factors, for example lifestyle, nutrition, physical activity, and vitamin D status may all influence peak bone mass, particularly for exposures during intrauterine and early infant life. As peak bone mass is a more important determinant of later osteoporosis risk than is age-associated bone loss, such early life considerations are important for later risk of fragility fracture, and have recently been recognized as such by the United Nations and World Health Organization. In women, oestrogen deficiency is a major pathogenetic factor in menopausal bone loss. In older men, oestrogen status is also sig nificantly related to bone mineral density levels whereas the rela tionship between age-related bone loss and declining testosterone levels is less prominent. In older people, vitamin D insufficiency and secondary hyperparathyroidism are common and contribute to age-related bone loss. Other potential pathogenetic factors include Fig. 20.4.1 Vertebral fracture (arrowed). 1500 1000 500 0 0 20 40 60 Bone loss and risk of osteoporosis Development of peak bone mass Age (yr) Bone mass (g/Ca) 80 100 Peak bone mass Fig. 20.4.2 Schematic representation of lifetime changes in bone mass in men and women. Reprinted from Cooper C, Melton LJ (1992). Epidemiology of osteoporosis. Trends Endocrinol Metab, 3, 224–229, Copyright © 1992, with permission from Elsevier.

 declining levels of physical activity and reduced serum levels of insulin-like growth factors. Pathophysiology The mechanical competence of the skeleton is maintained by the process of bone remodelling, in which a quantum of bone is re moved by osteoclasts followed by the formation, in the cavity so-created, of new bone by osteoblasts. Under normal circum stances resorption always occurs before formation and the amounts of bone resorbed and formed within each bone remodelling unit are similar. In menopausal bone loss, there is an increase in the number of bone remodelling units on the bone surface (increased remodel ling rate), resulting in a higher number than normal of remodelling units undergoing resorption at any one time. In addition, within each of these units less bone is formed than resorbed, leading to a negative remodelling imbalance. It is believed that one of the early, and probably transient, effects of oestrogen deficiency is to increase the activity of osteoclasts, at least in part by suppressing apoptosis. Increased osteoclastic activity causes an increase in the depth of erosion of bone by these cells, contributing to the trabecular pene tration and disruption of bone architecture that characterizes postmenopausal osteoporosis. Although bone mass and architec ture are important determinants of bone strength and fracture risk, other aspects of bone composition and structure also contribute. These include the composition of bone matrix and mineral, bone size, and bone geometry. In addition, increased bone turnover per se contributes to bone fragility, independently

of its effects on bone mass (Fig. 20.4.3). The pathophysiology of other forms of osteoporosis remains to be fully defined. In glucocorticoid-induced osteoporosis, reduced bone formation and low bone turnover predominate in those treated long term, but there is evidence that in the early stages of treatment there is an increase in bone turnover and osteoclast activity. The alterations in bone remodelling responsible for osteoporosis in men have not been established, but the lesser degree of structural disruption of cancel lous bone during ageing suggests that reduced bone formation plays a greater role in age-related bone loss in men than women. Whether this applies to men with osteoporosis, however, is uncertain. In recent years, several signalling pathways central to the regulation of bone remodelling have been defined. These include the receptor activator of NFkB ligand/osteoprotegerin (RANKL/OPG) pathway, which plays a major role in the regulation of osteoclast development and activity and has been exploited in the development of denosumab, a human monoclonal antibody to RANKL for the treatment of osteo porosis and other diseases associated with excessive bone resorption. Another is the Wnt signalling pathway, which regulates bone forma tion. Inactivating mutations of sclerostin, which inhibits the pathway, and activating mutations of low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor for the pathway, are associated with high bone mass and increased bone strength. Diagnosis and risk assessment Measurement of bone mineral density Bone mass can be assessed by several techniques, of which dual- energy X-ray absorptiometry is the gold standard and provides meas urements of bone mineral density in the spine and hip. According to the World Health Organization (WHO) operational classifica tion, osteoporosis is present when the bone mineral density (BMD) is 2.5 standard deviations or more below normal peak bone mass (T-score ≤ −2.5). Established osteoporosis is defined as a T-score less than or equal to −2.5 in association with a previous fragility fracture. Other approaches to assessment of bone mass include broadband ultrasound attenuation, quantitative computed tomography (QCT), and high resolution peripheral QCT (HRpQCT). The T-scores gen erated by these methods differ according to the device used and so cannot be used to diagnose osteoporosis in the same way as central dual-energy X-ray absorptiometry. Clinical risk factors In clinical practice bone mineral density values are used to predict fracture risk, in much the same way that blood pressure is used to predict stroke. Other clinical risk factors can also be used to improve prediction of fracture risk, since some of these act at least partly independently of bone mineral density. These include age, gluco corticoid therapy, a previous history of fracture, a family history of hip fracture, current smoking, alcohol abuse, and certain diseases as sociated with osteoporosis, for example rheumatoid arthritis (Table 20.4.1). An algorithm that uses these risk factors with or without Risk of falling Protective response Energy absorption Bone mineral density Bone turnover Bone size and geometry Bone structure and material Force of impact Bone strength Fracture risk Fig. 20.4.3 Pathogenetic factors for osteoporotic fractures. Table 20.4.1 Risk factors for osteoporosis BMD-independent BMD-dependent Age Untreated hypogonadism Previous fragility fracture Malabsorption Maternal history of hip fracture Endocrine disease Oral glucocorticoid therapy Chronic renal disease Current smoking Chronic liver disease Alcohol intake ≥3 units/day Chronic obstructive pulmonary disease Rheumatoid arthritis Immobility BMI ≤19 kg/m2 Drugs, e.g. aromatase inhibitors, androgen deprivation therapy Falls BMD, bone mineral density; BMI, body mass index.

 bone mineral density measurements to estimate 10-year fracture probability has been developed, originally with the WHO (FRAX, http://www.shef.ac.uk/FRAX) and enables intervention thresholds to be based on absolute risk rather than on bone mineral density T-scores. This approach has now been widely adopted globally with many guidelines using the

probability equivalent to a woman of the same age as the patient, with a prior fragility fracture, average body mass index (BMI) and no clinical risk factors and without BMD, in the FRAX model, as a threshold for therapeutic intervention. The setting of any threshold is of course arbitrary, but such an approach has been shown to be cost-effective, has the merit of adapting to local fracture epidemiology and not applying a fixed threshold at the extremes of age. For example, in the United Kingdom, the ‘inter vention threshold’ varies between 7% and 30% between the ages of 40 and 90 years. Other risk factors that are associated with low bone mineral density include untreated premature menopause, other causes of hypogonadism including treatment with aromatase inhibitors or gonadotrophin-releasing hormone analogues, low BMI, hyper thyroidism, and malabsorption. Recently proton pump inhibitors, thiazolidenediones, and selective serotonin receptor uptake inhibi tors have been associated with increased fracture risk, although it is uncertain whether this is mediated solely through reduced bone mineral density. Risk factors for falling are major determinants of fracture risk, particularly for hip fracture in older people (Fig. 20.4.3). Their recognition is important, since many are modifiable. They include poor visual acuity, neuromuscular weakness, and incoordination, reduced mobility, cognitive impairment, and the use of sedatives, tranquillizers, and alcohol. There are also many environmental haz ards that increase the risk of falling, such as uneven paving stones, poor lighting, and loose carpets and wires. Radiology Radiology also plays an important role in the diagnosis of osteo porosis, particularly in the case of vertebral fractures. Since only approximately 20–30% of these fractures come to medical atten tion lateral images of the spine obtained using X-ray or dual-energy X-ray absorptiometry may be the only means of diagnosis. Even though vertebral fractures may be asymptomatic in some individ uals, their diagnosis is important because of the high risk of future fractures, both in the spine and elsewhere, and the consequent need for treatment. Biochemical markers of bone turnover Biochemical markers of bone resorption [such as urinary deoxypyridinoline, pyridinoline, N-terminal and C-terminal cross- linked telopeptides of type I collagen (CTX)] and formation [such as osteocalcin, bone-specific alkaline phosphatase, N-terminal propeptide of type I procollagen (P1NP)] have been shown to be useful in the prediction of fracture risk, particularly when combined with bone mineral density measurements, and in the monitoring of response to treatment. An international consensus has sug gested that venous P1NP and fasting venous CTX should be used as the standard markers of bone formation and resorption respect ively. However, their role in clinical practice has not been firmly established. Differential diagnosis Secondary causes of osteoporosis should be excluded where appro priate. A full blood count, liver function tests, serum calcium and phosphate levels, thyroid function tests, plasma immunoelectro phoresis, and Bence-Jones protein determination should be per formed in the first instance with further investigation if indicated. In men, in whom secondary causes are more common, serum tes tosterone, gonadotrophins and prolactin, and 24-h urinary cortisol and/or a dexamethasone suppression test should also be performed. Pharmacological interventions General considerations Interventions that are approved for the prevention and treatment of osteoporosis are shown in Table 20.4.2. Most of these are ap proved only for the treatment of postmenopausal osteoporosis, but alendronate, etidronate, risedronate, zoledronic acid, and teriparatide also have licences for the prevention and/or treatment of glucocorticoid-induced osteoporosis and alendronate, risedronate, zoledronic acid, strontium ranelate, and teriparatide are approved for treatment of osteoporosis in men. Calcitriol is approved for osteoporosis in postmenopausal women but is little used and will not be considered further. Positioning of treatments Since there have been no head to head studies of these interven tions in which fracture has been a primary end-point, direct com parisons cannot be made of the magnitude of fracture reduction between drugs.

However, in the case of vertebral fracture, re ductions of around 30–70% are seen in postmenopausal women with osteoporosis after three years treatment with most interven tions. The evidence base for antifracture efficacy at nonvertebral sites does, however, differ between interventions, as shown in Table 20.4.3. Thus, only alendronate, risedronate, zoledronic acid, denosumab, and strontium ranelate have been shown to reduce vertebral and nonvertebral fractures, including hip fractures. This Table 20.4.2 Pharmacological interventions used in the prevention of osteoporotic fractures Intervention Dosing regimen Route of administration Alendronate 70 mg once weekly 5 or 10 mg once daily Oral Etidronate 400 mg daily for 2 weeks every 3 months Oral Ibandronate a 150 mg once monthly Oral Ibandronate b 3 mg once every 3 months Intravenous injection Risedronate 35 mg once weekly 5 mg once daily Oral Zoledronic acid 5 mg once yearly Intravenous infusion Denosumab 60 mg every 6 months Subcutaneous injection Raloxifene 60 mg once daily Oral Strontium ranelate 2 gm once daily Oral Teriparatide 20 µg once daily Subcutaneous injection

SECTION 20 Disorders of the skeleton 4700 distinction is important because once a fracture occurs, the risk of a subsequent fracture at any site is increased independent of bone mineral density, and hence an intervention that covers all major fracture sites is preferable. Because of their broader spectrum of antifracture efficacy, alendronate, risedronate, zoledronic acid, and denosumab are generally regarded as front-line options in the prevention of fractures in postmenopausal women. Strontium ranelate is less frequently used now, despite good evidence of ef ficacy, largely due to concerns regarding increased risk of deep vein thrombosis and cardiovascular events. Since reduction in hip fracture risk has not been shown for raloxifene or ibandronate, these drugs are generally considered second-line options. Where intravenous therapy is required, for example in patients with malabsorption, intravenous zoledronic acid and subcutaneous denosumab are now the treatments of choice because they have a strong evidence base and require only once or twice-yearly ad ministration, respectively. Finally, the use of teriparatide may be limited by its cost to women with severe vertebral osteoporosis who are intolerant to or appear to be unresponsive to other treatments. Rate of onset of treatment effect Reduction in fracture risk has been shown to occur within one year of treatment for bisphosphonates and strontium ranelate. This is particularly important in the case of vertebral fractures, since after an incident vertebral fracture there is a 20% risk of a further fracture occurring within the next 12 months, emphasizing the importance of prompt treatment once a fracture has occurred. Duration of therapy The optimum duration of treatment is uncertain. There are poten tial concerns that long-term treatment with potent antiresorptives may increase bone microdamage and suppress its repair, possibly resulting in increased bone fragility. The risk of atypical femoral fractures with long-term antiresorptive therapy has emerged over recent years, and while the number of fragility fractures prevented by treatment substantially outweighs the number of atypical frac tures potentially caused, this has informed current approaches to treatment duration. Such concerns must be balanced against the possibility that increased bone turnover and bone loss after with drawal of therapy may result in increased fracture risk. The current consensus is that treatment should be continued for a minimum of five years; in those who remain at high risk (based on bone mineral density levels and/or incident fractures during treatment), longer treatment periods are likely to be indicated. Compliance and persistence As is the case with many other chronic conditions, compliance and persistence with treatment for osteoporosis are poor: approxi mately 50% of patients do not follow their prescribed treatment regimen and/or discontinue treatment within one year. Patient edu cation is important in this respect and nurse-led monitoring early in the course of treatment has been shown to improve

compliance. Whether monitoring by measurement of biochemical markers of bone turnover of bone mineral density provides additional benefits has not been established. Current pharmacological therapeutic options for osteoporosis Bisphosphonates The bisphosphonates are synthetic analogues of the naturally occurring compound pyrophosphate and inhibit bone resorp tion. Oral bisphosphonates are generally well tolerated. Upper gastrointestinal side effects may occur with nitrogen-containing bisphosphonates (alendronate, risedronate, and ibandronate), par ticularly if the dosing regimen is not adhered to. It is therefore im portant that patients take the drug according to the instructions, namely in the morning with a full glass of water, 45 min before food, drink, or other medications, and remaining upright for 30–60 min after the dose. Ibandronate is available as an oral or intravenous for mulation. The latter is given as an injection over 15–30 seconds every three months. Zoledronic acid is given once yearly in a dose of 5 mg by intravenous infusion over a minimum of 15 minutes. An acute phase reaction may occur with intravenous bisphosphonate admin istration, particularly with the first injection, resulting in flu-like symptoms for 24–48 hours; the severity and frequency of this can be reduced by administration of paracetamol on the day of the infusion and the subsequent one to two days. Osteonecrosis of the jaw is a very rare side effect of bisphosphonate therapy; cases tend to be in patients with dental disease who have undergone invasive dental procedures. Strontium ranelate Strontium ranelate is composed of two atoms of stable strontium with ranelic acid as a carrier. Although its mechanism of action re mains to be fully defined, there is some evidence that it both in hibits bone resorption and stimulates bone formation. Treatment is associated with a substantial increase in BMD in the spine and hip, although part of this increase is artefactual and due to incorpor ation of strontium into bone. Strontium ranelate is taken as a single daily dose and is generally well tolerated. There is a small increase in the frequency of diarrhoea, nausea, and headache. There ap pears to be an increased risk of deep vein thrombosis, and recently treatment with strontium ranelate was associated with increased Table 20.4.3 Spectrum of antifracture efficacy of pharmacological interventions for osteoporosis Intervention Vertebral fracture Nonvertebral fracture Hip fracture Alendronate + + + Denosumab + + + Etidronate + nae nae HRT + + + Ibandronate + +a nae Raloxifene + nae nae Risedronate + + + Strontium ranelate + + +a Teriparatide + + nae Zoledronic acid + + + a Post hoc analysis in subset of patients. Nae, not adequately evaluated.

 cardiovascular events; its use has been limited to those with high fracture risk and low cardiovascular risk, and the therapy is now no longer manufactured by Servier. Raloxifene Raloxifene is a selective oestrogen-receptor modulator which has oestrogenic (antiresorptive) effects in the skeleton without the un wanted effects of oestrogen in the breast and endometrium. It is taken orally as a single daily dose and has been associated with a sig nificant decrease in the risk of breast cancer. Adverse effects include leg oedema, leg cramps, hot flushes, and a two to threefold increase in the risk of venous thromboembolism. Denosumab Denosumab is the most recently licensed antiresorptive therapy and is administered as a six-monthly subcutaneous 60 mg injection. It inhibits the RANK-RANKL-OPG pathway and thus the activation of osteoclasts. It effectively increases bone mineral density and re duces the incidence of fractures at the spine, hip, and other sites. Its major advantage is that it appears safe in mild to moderate renal impairment and therefore may provide opportunities for use where oral or intravenous bisphosphonates are contraindicated. Atypical femoral fractures and osteonecrosis of the jaw may rarely occur in association with denosumab therapy for osteoporosis. Parathyroid hormone peptides Teriparatide (recombinant human 1–34 parathyroid hormone) is administered by subcutaneous injection in daily doses of 20 µg. It has anabolic effects on bone, increasing bone

formation and pro ducing large increases in bone mineral density in the spine. Side ef fects include nausea, headache, and dizziness; in addition, transient hypercalcaemia and hypercalciuria may occur. Hormone replacement therapy (HRT) Because the risk/benefit balance of HRT is generally unfavour able in older postmenopausal women, it is regarded as a second- line treatment option. However, it is a potential option in younger postmenopausal women at high risk of fracture, particularly those with vasomotor and other menopausal symptoms. Calcium and vitamin D Available evidence does not support a role for calcium and vitamin D alone in prevention of osteoporotic fractures except in the in stitutionalized older population. However, calcium and vitamin D supplements should be co-prescribed with other treatments for osteoporosis since the evidence base for their antifracture efficacy is derived from studies in which calcium and vitamin D were routinely administered. Novel pharmacological therapies Increased understanding of the molecular basis of bone biology has led to the ongoing development of several potential new therapies, which are currently in clinical testing. Odanacatib is a once weekly oral treatment which inhibits cathepsin-K, a cysteine protease ex pressed in osteoclasts which degrades type 1 collagen and has been shown to increase bone mineral density and reduce fracture incidence in postmenopausal women. A second area of develop ment is that of sclerostin inhibition via use of specific humanized monoclonal antibodies. Sclerostin is secreted by osteocytes and negatively regulates bone formation via the LRP5/Wnt signalling pathway. Inhibition of this negative influence by antibodies such as blosozumab and romosozumab has been shown to lead to increases in bone mineral density at the lumbar spine and hip sites. Nonpharmacological interventions Falls have an important role in the pathogenesis of fragility frac tures, particularly in the frail and old. Multiple medical and envir onmental factors increase the risk of falling and many of these are modifiable. Multifaceted interventions have been shown to reduce the frequency of falling although reduction in fractures has not been convincingly demonstrated. Several lifestyle measures improve bone health including adequate dietary calcium intake and main tenance of a normal vitamin D status. Appropriate levels of exercise should be recommended, and smoking and alcohol abuse discour aged. Physiotherapy and pain relief play important roles in the man agement of fractures. Glucocorticoid-induced osteoporosis Osteoporosis is a common complication of oral glucocorticoid therapy. Bone loss is most rapid during the first few months of therapy, during which there is also a rapid increase in fracture rate. Observational data indicate that increased fracture risk is seen at all doses of oral prednisone, even those below 5 mg of oral prednis olone daily; higher doses are associated with more rapid bone loss and higher fracture risk. The effects of inhaled glucocorticoids on bone are less certain but are potentially of great importance given their high level of use in the population. Cross-sectional data indi cate that adverse effects on bone mineral density may occur, particu larly when high doses are administered long-term. In both adults and children, a small increase in relative risk of fracture has been demonstrated with inhaled glucocorticoid use, but because similar increases are seen in those using only bronchodilators, it is likely that the underlying illness rather than the glucocorticoids per se is responsible for the observed increase. In the context of glucocorticoid-induced osteoporosis, the term primary prevention is used to denote initiation of bone protective therapy at the time glucocorticoids are initiated, whereas secondary prevention implies that bone protection is started later in the course of glucocorticoid therapy. This distinction is important because of the rapid onset of bone loss and increase in fracture risk after gluco corticoid initiation, providing a strong rationale for early interven tion in high-risk individuals. Although several interventions have been evaluated in the prevention and treatment of glucocorticoid- induced osteoporosis, the evidence base is much less robust than that which exists in postmenopausal women. Nevertheless, there is reasonable evidence that alendronate,

risedronate, etidronate, zoledronic acid, and teriparatide are effective, and these are ap proved for this indication. Guidelines for the management of glucocorticoid-induced osteo porosis originally focused on a T-score threshold of −1.5, reflecting

SECTION 20 Disorders of the skeleton 4702 the altered BMD fracture relationship with glucocorticoid treat ment. With the advent of assessment of absolute probability using the FRAX calculator, an international framework for such guide lines has been published with glucocorticoids assessed as part of overall fracture risk. These take as their starting point men and women aged 18 years or over in whom oral glucocorticoid therapy is considered for three months or longer; intervention is based on absolute probability thresholds, incorporating the additional glucocorticoid dose effect, and set appropriately for local and na tional considerations. Conclusion In the last few decades, the perception of osteoporosis as an inevitable consequence of ageing has been replaced by an understanding of the complex pathophysiology of what is a devastating, but treatable disease. Advances in the epidemio logical characterization of the determinants of fracture risk across lifecourse, geographic location, and time; development of effective strategies to assess individualized fracture risk; and the availability of a range of effective pharmacological therapies, all demonstrate the immense progress that has been achieved within this field. Challenges remain, not least the substan tial gap between fracture occurrence and subsequent treatment for osteoporosis, but such issues are being addressed internation ally. Future demographic shifts towards an increasingly elderly population globally will ensure that such work remains essential in decades to come. FURTHER READING Boonen S, et al. (2005). Effect of osteoporosis treatments on risk of nonvertebral fractures: review and meta-analysis of intention-to- treat studies. Arch Osteoporos., 12, 43. Compston JE, McClung MR, Leslie WD (2019). Osteoporosis. Lancet, 393, 364–76. Compston J, et al. National Osteoporosis Guideline Group (2017). UK clinical guideline for the prevention and treatment of osteoporosis. Maturitas, 75, 392–6. Compston JE, Seeman E (2006). Compliance with osteoporosis therapy is the weakest link. Lancet, 368, 973–4. Cranney A, et al. (2006). Clinical Guidelines Committee of Osteoporosis Canada. Parathyroid hormone for the treatment of osteoporosis: a systematic review. Canadian Medical Association Journal, 175, 52–9. Cummings SR, Melton III LJ (2002). Epidemiology and outcomes of osteoporotic fractures. Lancet, 359, 1761–7. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group (2010). Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ, 340, b5463. Harvey N, Dennison E, Cooper C (2010). Osteoporosis: impact on health and economics. Nat Rev Rheumatol, 6, 99–105. Hernlund E, et al. (2013). Osteoporosis in the European Union: med ical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos, 8, 136. Johnell O, Kanis JA (2006). An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International, 17, 1726–33. Kanis JA (2002). Diagnosis of osteoporosis and assessment of fracture risk. Lancet, 359, 1929–36. Kanis JA, et al.; Task Force of the FRAX Initiative (2011). Inter pretation and use of FRAX in clinical practice. Osteoporos Int, 22, 2395–411. Kanis JA, et al.; Scientific Advisory Board for the European Society for Clinical and Economic aspects of Osteoporosis (ESCEO) and the Committee of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF) (2019). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int, 30, 3–44. Lekamwasam S, et al.; Joint IOF-ECTS GIO Guidelines Working Group (2012). A framework for the development of guidelines for the man agement of glucocorticoid-induced osteoporosis. Osteoporos Int, 23, 2257–76. Lock CA, et al. (2006). Lifestyle interventions to prevent osteoporotic

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