Ministry of Defence

Synopsis of Causation

Osteoporosis
(incorporating Osteopenia)

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1 Osteoporosis is by far the most common of the metabolic bone diseases, constituting a major cause of morbidity and mortality. It is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in fracture risk. Fractures due to osteoporosis most frequently affect the vertebrae, femoral neck, and distal radius (i.e. spine, hips, and forearms).

1.2 An expert panel of the World Health Organization (WHO) has proposed diagnostic criteria for osteoporosis, based on measurements of the **bone mineral density (BMD)**. Osteoporosis is defined by a BMD value that lies 2.5 standard deviations (SD) or more below the average value for the healthy young adult population. The term osteopenia is used to describe a less advanced state in which the BMD value lies between 1 SD and 2.5 SD below the average value for the healthy young adult population. The risk of fracture is less for individuals with osteopenia than for those with osteoporosis, but the relationship between BMD and fracture appears to be one of a gradient in risk as opposed to a threshold.

1.3 The scale of the problem is illustrated by the fact that approximately 30% of postmenopausal women have osteoporosis as defined by the WHO. It is estimated that approximately 70% of hip fractures are attributable to osteoporosis. The excess mortality associated with hip fractures is estimated to range from 12-20%,[1] and 50% of the survivors will fail to regain independence in their own homes.

2. Clinical Features

2.1 Bone mass decreases with increasing age and, in women, with the time that has elapsed since the menopause. However, although osteoporosis is particularly common in older postmenopausal women, and is more common in the white and Asian population than in black people, it can affect individuals of all ages, all races, and both sexes.

2.2 Osteoporosis remains clinically silent until manifested by a fracture or by height loss. Osteoporosis may be suspected on clinical grounds where a fracture results from trauma that would not normally be expected to result in bony damage. Common fracture sites involve:

- **Vertebrae:** single or multiple compression fractures of the vertebrae are the most common indicator of osteoporosis. Radiological findings range from anterior wedging to complete vertebral collapse
- **Hip:** most fractures are in the femoral neck or at the base of the greater trochanter
- **Forearm:** Colles' fracture of the distal radius, caused by a fall on the outstretched hand

There is an increasing recognition that osteoporosis can lead to fractures at other anatomical sites, including the ribs, humerus, tibia, pelvis, and elsewhere in the femur. Indeed, any low-energy fracture in a person >50 years should be regarded as osteoporosis until excluded by densitometry.

2.3 Many patients with compression fractures of the vertebrae are asymptomatic, particularly those who have anterior wedging only. However, collapse of the vertebral bodies, which most commonly affects the lower thoracic and upper lumbar regions, can cause back pain and loss of stature. An increased curvature of the thoracic spine (kyphosis) with loss of the normal lumbar lordosis may become evident as a rounding of the spine, known colloquially as a "dowager's hump".

2.4 Fractures related to osteoporosis, especially those of the hip, can adversely affect the subsequent quality of life. Many patients are unable to resume their former lifestyle and one person out of every 4 to 5 who sustains a hip fracture does not survive more than one year after the fracture.[2]

2.5 Prior to the occurrence of a fracture, an individual's clinical features do not provide a reliable predictor of bone status and fracture risk. The measurement of BMD is the primary test involved in the diagnosis of osteoporosis. Plain x-rays lack the sensitivity to diagnose osteoporosis until total bone density has been reduced by 40-50%. The method of choice for determining BMD is dual-energy x-ray absorptiometry (DXA), whilst heel ultrasound and quantitative computerised tomography are also used. Each standard deviation reduction in the BMD score found on screening equates to a 10-15% reduction in BMD and an approximate doubling of fracture risk. Thus, the fracture risk is increased even before the process has progressed sufficiently to satisfy the WHO definition for osteoporosis.[2]

2.6 Factors other than BMD also play a role in determining the fracture risk. These include bone turnover, bone geometry, and the "non-skeletal" factors that influence the risk of falls, such as **muscle strength, balance,** and **visual acuity**.

3. Aetiology

3.1 Osteoporosis may be either primary or secondary. In **primary osteoporosis**, a reduction in bone mass occurs unconnected to any other chronic illness. **Type 1 osteoporosis** occurs in **postmenopausal women** in association with oestrogen deficiency, whilst **senile (type 2) osteoporosis** affects the elderly of both sexes and is due to the general effects of ageing. Primary osteoporosis is influenced by heredity and by antecedent environmental factors. In contrast, **secondary osteoporosis** develops as a direct consequence of some specific condition that influences bone mass. Some patients are affected by **combinations of primary and secondary causes**.

3.2 **Primary osteoporosis:** Skeletal bone mass increases during puberty and young adult life, peaks at age 25, and then generally remains stable for some years because resorption and formation are equal. Subsequent menopausal and age-related bone loss reflects an imbalance between resorption and formation. Differential bone loss may occur in different parts of the skeleton. In women, bone loss may begin well before the menopause, particularly in the region of the distal radius.

3.3 Decreased bone mass and increased fragility can occur as a consequence of:

- failure to achieve optimal peak bone mass
- bone loss caused by increased bone resorption
- inadequate replacement of lost bone due to decreased bone formation

These mechanisms are influenced by a wide variety of factors as follows:

3.3.1 **Genetic factors:** The skeletal determinants of osteoporotic fracture risk, such as BMD, ultrasound properties of bone, skeletal geometry and bone turnover are all subject to strong genetic influence. It has been estimated that 60-85% of the variance in BMD is genetically determined, and hereditary estimates for femoral neck geometry and bone turnover markers range from 50-80%. In comparison, the heritability of fracture itself is relatively low at 25-35%, reflecting the importance of fall-related factors in the pathogenesis of fracture.

Rarely, osteoporosis arises as a result of mutation in a single gene. However, the genetic factors are more usually under polygenic control. A number of candidate genes have been studied and polymorphisms in genes for the vitamin D receptor, oestrogen receptor-α, transforming growth factor-β 1, and *COLIA1* (gene encoding type I collagen) have all been identified as potential genetic markers for osteoporosis. For the most part, the causative genes have yet to be identified.[3]

3.3.2 **Gonadal hormones:** a number of hormones play an important part in the development of osteoporosis, most notably the gonadal steroids. Oestrogen deficiency from natural or surgically induced menopause accelerates bone loss. Women with late menarche and/or premature menopause (<age 45) have a shorter exposure to normal reproductive hormones, and may be at increased risk.[4] Androgen deficiency may be important in both women and men. Testosterone is converted to oestrogen in the male and hence a lowering of testosterone contributes to osteoporosis in men.

3.3.3 **Other hormones** may play a role in age-related bone loss, including increased levels of parathyroid hormone, often consequent on dietary calcium and Vitamin D deficiency, and decreased secretion of growth hormone with consequent decrease in levels of circulating insulin-like growth factor I.

3.3.4 **Local factors**: Systemic hormones that influence the skeleton (including oestrogen and parathyroid hormone) alter the production of local factors e.g. cytokines, prostaglandins, and growth factors. Tissue levels of insulin-like growth factor-binding proteins, transforming growth factor-β, and bone morphogenetic protein may play a role in osteoporosis.[5]

3.3.5 **Nutritional and lifestyle factors**

- **High levels of physical activity and good calcium intake** during childhood and puberty can help achieve maximal bone mass.[5] An adequate dietary intake of calcium and vitamin D and a physically active lifestyle in the later decades of life may also translate into a reduction in the risk of osteoporosis.[4] Deficiency of other dietary factors such as protein and vitamin K may also contribute to the risk of developing osteoporosis.[6]
- **Low body weight** is an important risk factor. The positive relationship between a high body weight and an increased BMD may be attributable in part to increased mechanical forces on the bone, but may also relate to other factors such as conversion of adrenal androgens to oestrogens in fat. The association between low body weight and osteoporotic fracture may be partially attributable to non-skeletal factors such as decreased padding of the hip and decreased muscle strength.[5]
- **Smoking** is associated with lower BMD and increased fracture risk
- **Modest alcohol intake** (i.e. 3-4 units per week in women) has been associated with a positive effect on BMD. High alcohol intake is detrimental

3.3.6 **Juvenile osteoporosis**, with onset between the ages of 8 and 14 years, is a rare disease that usually remits spontaneously. Osteoporosis occurring in premenopausal women or younger men with no obvious secondary cause is termed **idiopathic osteoporosis**. Some patients with idiopathic osteoporosis have a transient, self-limiting condition, whilst in others the course is progressive and disabling.

3.4 **Secondary osteoporosis** is associated with specific conditions including:

3.4.1 **Oral corticosteroids:** The most common form of secondary osteoporosis is that induced by treatment with corticosteroids. Oral corticosteroid treatment using more than 5mg of prednisolone or equivalent daily leads to a reduction in BMD and an increase in fracture risk. This risk increases rapidly after the start of oral corticosteroid therapy (within 3 to 6 months) and declines after stopping treatment.[7]

3.4.2 **Inhaled corticosteroids:** The effect of the inhaled corticosteroids, used in the treatment of asthma and chronic obstructive pulmonary disease, is more controversial. There is increasing evidence that there may be an elevated risk of osteoporosis and fractures in patients who take inhaled corticosteroids, although

primarily at high doses that affect the hypothalamic-pituitary-adrenal axis.[8] A meta-analysis incorporating results from 11 studies reported that budesonide at a mean daily dose of 686 µg (standard deviation (SD)158 µg), beclomethasone dipropionate at 703 µg (SD 123 µg), and triamcinolone at 1000 µg (SD 282 µg) were found to affect bone mineral density and markers of bone formation.[9] Amongst subjects followed for over 8 years in a case-control study of elderly patients, the rate of hip fracture was only elevated with daily doses of more than 2,000 µg of inhaled corticosteroids, and was not elevated at any dose of nasal corticosteroids. Consequently, this particular study concluded that the long-term use of inhaled corticosteroids at the usual recommended doses is not associated with a risk of fracture in older patients with respiratory disease.[10]

3.4.3 **Other drugs:** Osteoporosis has been associated with an extensive list of other drugs that includes heparin anticoagulation, anticonvulsants (including phenytoin, barbiturates and carbamazepine), methotrexate, cyclosporine A, medroxyprogesterone acetate (used as a depot contraceptive), luteinising hormone-releasing hormone agonists, lithium, and aluminium-containing antacids.[11]

3.4.4 **Diabetes mellitus:** Adolescents with type 1 (insulin-dependent) diabetes mellitus may fail to attain optimal peak bone mass, thus increasing the risk of osteoporosis in later life.[12] The position regarding adults with type 2 (non-insulin-dependent) diabetes mellitus is less clear. The tendency to obesity in these individuals may confer a degree of relative protection. It is not known whether adolescents with type 2 diabetes will demonstrate a low bone mass.[13]

3.4.5 **Hypogonadism** can occur in both men and women, and has multiple causes. Rapid bone loss occurs both in patients with **primary hypogonadism** due to ovarian or testicular failure, and those with **secondary hypogonadism** related to hypothalamic or pituitary disease. This latter group includes patients who are suffering from **anorexia nervosa**, although in this case other factors including undernutrition also play a part. Some female athletes develop **athletic amenorrhoea** due to oestrogen deficiency, thus becoming prone to osteoporosis despite the high levels of physical activity that they undertake.

3.4.6 **Other endocrine disorders** associated with osteoporosis include Cushing's syndrome, hyperparathyroidism, acromegaly, prolactinoma, growth hormone deficiency, and hyperthyroidism (primary hyperthyroidism or excessive treatment with thyroid hormone).

3.4.7 **Rheumatoid arthritis and ankylosing spondylitis:** Patients with rheumatoid arthritis have an increased incidence of osteoporosis, thought to be related to inflammation and immobilisation as well as the use of corticosteroids. Osteoporosis is also a common complication of ankylosing spondylitis where the bone loss is largely confined to the axial skeleton, contrasting with rheumatoid arthritis where the loss in more marked in peripheral bone.[14,15]

3.4.8 **Immobilisation:** Prolonged immobilisation leads to **disuse osteoporosis**, which may be localised or generalised. The skeleton is sensitive to mechanical loading, and a significant loss of bone will ensue from an absence of weight bearing activity, for example as a consequence of prolonged bed rest, paralysis,

application of a cast to treat a fracture, or long duration space missions. Statistically significant decreases in BMD of the humerus have been observed after 6 weeks of immobilisation following soft-tissue shoulder surgery.[16] Animal studies have also shown decreased tibial shaft BMD after 6 weeks of unilateral hind limb immobilisation.[17] Bone mineral that has been lost because of disuse may be restored upon return to normal activity, although most cases of disuse osteoporosis require a long time for bone to recover.[18] In animal models it has been shown that recovery may not be complete and/or may take longer than the time course of the original bone loss.[19] In a study of patients who had suffered a stroke, BMD in the proximal femur was reduced on the affected side when measured twelve months after the event. The scale of the reduction was greater in those who remained confined to a wheelchair than in those who had been ambulant throughout or who had relearned to walk within two months.[20]

3.4.9 **Gastrointestinal disease:** Decreased BMD is a frequent finding in several gastrointestinal conditions, having been reported in:

- Crohn's disease
- Ulcerative colitis
- Coeliac disease
- Gastrectomy
- Pernicious anaemia

The link appears to be multifactorial, involving malabsorption of vitamin D, calcium and possibly vitamin K and other nutrients; treatment with corticosteroids; inflammatory cytokines in inflammatory bowel disease; and hypogonadism induced by gastrointestinal disease.[21]

3.4.10 **Miscellaneous conditions:** A number of other conditions have been identified as causes of osteoporosis, including the following:

- Total parenteral nutrition
- Severe malnutrition
- Vitamin C deficiency (scurvy)
- Severe alcohol abuse – associated with poor nutrition, leanness, liver disease, malabsorption, vitamin D deficiency and hypogonadism. This situation contrasts with the finding that moderate intake of alcohol has a beneficial effect on BMD,
- Sickle cell disease and thalassaemia
- Chronic renal failure
- Chronic hepatic disorders
- Connective tissue disorders, including Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' disease, and homocystinuria
- Organ transplantation - occurring as a result both of the underlying disease process and the immunosuppressant drugs used to prevent graft rejection
- HIV infection – occurring as a result both of disease related factors and the antiretroviral drugs used to treat the condition

3.4.11 **Trauma:** Reflex sympathetic dystrophy, which may follow localised trauma, stroke or peripheral nerve injury, can give rise to osteoporosis in association with vasomotor instability and hyperaesthesia. Otherwise, physical trauma has

not been identified as an aetiological factor in osteoporosis. Fractures are a result of the disease process rather than its cause.

3.4.12 **Gulf illness:** Assertions have been made that vaccinations given to military personnel who served in the Persian Gulf during the 1990/91 conflict (or who were vaccinated but were not subsequently deployed) may be associated with osteoporosis. It has been reported that bone biopsies taken from 17 Gulf War veterans who were seeking litigation demonstrated a significant reduction in bone formation at both the cellular and tissue level. The clinical relevance of this observation remains to be established.[22] One theoretical explanation implicates vasoactive neuropeptides, substances that play a protective role against autoimmune and inflammatory diseases. It has been suggested that interactions and potential synergistic effects occurring between infections, vaccines, and their adjuvants may initiate autoimmune mechanisms that impair vasoactive neuropeptide function. The theory goes on to propose that the effects of this process may include disturbed calcium metabolism.[23] At present this explanation remains hypothetical, and further work is required to substantiate and investigate the suggested link between osteoporosis and service in the Persian Gulf.

4. Prognosis

4.1 Prevention of osteoporotic-related fractures is dependent in the first instance on an ability to detect low bone mass within individuals, including those who are asymptomatic. The frequency of diagnosis thus depends on the frequency, site, and timing of bone density measurements. The goal of subsequent osteoporosis treatment is to reduce fracture risk.

4.2 A history of a previous osteoporotic fracture acts as a risk factor for further fractures. For example, a history of a previous osteoporotic vertebral fracture increases the likelihood of another spine fracture fourfold, and of a hip fracture by a factor of two. The increased incidence is apparent within one year.

4.3 General nutritional and lifestyle measures are appropriate for all patients, whilst drug treatment is most clearly indicated in those cases in which a high current fracture risk has been identified. The following measures feature amongst those that have been advocated:

- An adequate intake of calcium and vitamin D is an important component of a general programme of skeletal health, particularly in older women, although simply providing calcium and vitamin D alone will not prevent osteoporosis[24]
- The value of exercise as an intervention for the prevention of postmenopausal bone loss remains controversial. Modest evidence suggests that exercise may be beneficial
- Agents that inhibit bone resorption, such as oestrogen (administered as hormone replacement therapy to postmenopausal women), bisphosphonates (including etidronate, alendronate and risedronate), and calcitonin
- Agents that increase bone formation, such as parathyroid hormone

4.4 Therapeutic measures to combat osteoporosis need to be complemented by measures to reduce both the frequency and effects of falls.

5. Summary

5.1 Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in fracture risk. The disease constitutes a major cause of morbidity and mortality.

5.2 The reduction in bone mass that occurs in primary osteoporosis is unconnected to any other chronic illness, being principally associated with oestrogen deficiency in postmenopausal women, and the general effects of ageing in the elderly of both sexes. Secondary osteoporosis develops as a direct consequence of some specific condition that influences bone mass.

5.3 Prevention of osteoporotic-related fractures is dependent in the first instance on an ability to employ screening techniques to detect low bone mass. Treatment strategies are aimed at arresting bone loss, preserving microarchitecture, and reducing fracture risk.

6. Related synopses

7. Glossary

adjuvant	A substance added to a vaccine to improve the immune response.
androgen	General term for any male sex hormone.
bone morphogenetic protein	Proteins that induce the formation of cartilage and bone.
calcitonin	A hormone that causes a reduction of calcium ions in the blood, the opposite effect to parathyroid hormone (q.v.).
corticosteroids	A group of synthetic hormones that are used therapeutically in a number of illnesses for their anti-inflammatory activity.
Cushing's syndrome	An increased concentration of glucocorticoid hormone in the bloodstream, produced by a benign tumour of the adrenal gland.
cytokines	Proteins that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types, rather than specialist glands.
distal radius	The further extremity the radius (one of the two bones of the forearm).
femoral neck	The short, constricted portion of the thigh bone (femur), lying between the femoral head and the trochanters.
gonadal	Pertaining to the ovary or testicle.
greater trochanter	A large bony protuberance at the upper end of the shaft of the thigh bone (femur).
insulin-like growth factor I (IGF-I)	Hormone that stimulates the growth of bone and muscle in adults, released from the liver in response to growth hormone.
insulin-like growth factor-binding proteins	A family of proteins that bind insulin-like growth factors and modulate their actions at the cellular level.
lumbar lordosis	Forward (inward) curvature of the lower part of the vertebral column.
parathyroid hormone (PTH)	A hormone produced in the parathyroid glands that increases blood calcium levels, the opposite effect to calcitonin (q.v.).

phenotype	What an organism looks like as a result of the interaction between its genetic constitution and the environment. Hence *phenotypic*.
polygenic	Relating to an inheritable character that is controlled by several genes at once.
polymorphism	The presence of several distinct forms of a gene or phenotypic trait within a population with frequencies greater than 1%.
transforming growth factor-β	Factor synthesised in a wide variety of tissues that acts to induce phenotypic (q.v.) transformation.
vasomotor	Affecting the calibre of a blood vessel.

8. References

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