OSTEOPOROSIS

BONE STRUCTURE AND METABOLISM

Types of Bone

There are two types of bone namely cortical (compact) and cancellous (trabecular) bone. Bone consists of a dense outer cortical layer which encloses the cancellous bone. Cancellous bone consists of trabecular plates which interconnect with each other and with the inner aspects of the cortical bone. These trabecular plates are orientated along lines of stress.

Composition of bone

Bone consists of an organic matrix, bone cells and a mineral element. The matrix is composed of collagen fibres (mainly type I collagen) and which are laid down by osteoblasts. Collagen contains hydroxyproline which is released during collagen breakdown and can be measured in the urine as an index of bone activity. Other important proteins include osteocalcin which can also be measured to indicate the rate of bone turnover (see later).

The mineral element of bone is calcium and phosphate in the form of hydroxapatite crystals. Individual crystals are very small and are orientated along the lines of the collagen fibres.

Metabolic activity takes place on the surface of bone. The surface area of cortical bone is 10 fold less than the surface area of cancellous bone. This is one reason that osteoporosis presents earlier and is more marked in cancellous than cortical bone.

All bony surfaces are covered by endosteal cells. Bone remodelling starts with the attraction of a number of mononuclear (macrophage) cells from the blood to a bone surface. These cells then differentiate into osteoclasts which are then responsible for bone resorption. This occurs roughly every 10 seconds somewhere on a bony surface. What controls this activation is unknown but fatigue fractures, parathyroid and thyroid hormones play a role. The gonadal hormones and calcitonin are inhibitors.
Later a second cell, the osteoblast, replaces the osteoclast and is responsible for new bone formation and mineralisation.

**Erosion of bone**

A group of activated osteoclasts excavate an erosion cavity to a depth of 40-60um over 4-12 days, first by lowering the Ph under the osteoclast. This solubilizes the mineral phase of the bone (calcium etc.). Then the production of acid proteases allows the enzymatic degradation of the remaining organic components including the collagen. Over the next 7-10 days a layer of a cement substance is deposited which is rich in acid phosphatase, glycoproteins and proteoglycans. This is called the reversal phase. Once this has taken place a process called coupling attracts osteoblasts to the eroded surface where they form a sheet of cells over the eroded surface and excrete layers of osteoid matrix. A few days later this osteoid undergoes mineralisation.

Alkaline phosphatase is actively excreted by the osteoblasts at this stage. Osteocalcin (bone gla protein) is another mineralisation protein exclusively excreted by osteoblasts. This process is called a bone structural unit (BSU) and takes about 6 months to complete. About 10% of the bone surfaces are remodelling at any one time. In cancellous bone a BSU is 40-60um thick 0.5-1mm² in diameter. With oestrogen deficiency this cellular activity is increased 2 to 3 fold. Also the number of osteoclasts per BSU is increased 2-3 fold. The importance of this is that the depth of the erosion is increased and can penetrate the full thickness of the trabecula. If this happens it cannot be replaced. Further the osteoblasts that follow have a suboptimal performance. They have oestrogen receptors which must be activated for optimal osteoblast activity. In osteoporosis each remodelling sequence is associated with a small but finite deficit in bone.

In postmenopausal osteoporosis and with immobilization there is a marked loss of trabecular numbers whereas in steroid induced osteoporosis the trabeculae are reduced in thickness but a scaffolding of bone remains.
Biochemical Assessment of Osteoporosis

Serum and Urine Calcium

In uncomplicated osteoporosis calcium and phosphate are not disturbed. Hypercalciuria if present represents increased intestinal absorption or markedly accelerated bone erosion as in the hypercalciuria of immobilisation. The fasting urinary excretion of calcium is decreased by treatments which decrease bone erosion, increase bone formation or both. This can be used to monitor treatment.

Bone Alkaline Phosphatase (BAP)

BAP is the most commonly used biochemical marker of skeletal disease activity, and is actively excreted by osteoblasts. In osteoporosis, BAP may be moderately increased for several reasons. In the early menopause the BAP can be increased 2 fold due to the generalised increased bone turnover. Raised BAP is a marker of osteoblast activity and hence bone formation (as part of bone turnover).

Urine-Deoxypyridinoline (U-DPD)

Pyridinolines are cross-links between adjacent collagen molecules. The excretion of these in the urine is a marker of bone resorption.

Hydroxyproline

Most hydroxyproline found in the urine comes from the breakdown of collagen. Values are expressed in relation to creatinine excretion to eliminate the confounding effect of varying urine concentrations. Increased values occur with increased bone breakdown. Dietary sources must be excluded by a 48 hour collagen free diet (no meat, gelatin, bananas etc) and the urine collected must be the second morning voided sample.
Osteocalcin (S-GLA Protein)

This is believed to be exclusively synthesised by osteoblasts. There is a significant correlation and the serum values of osteocalcin.

**OSTEOPOROSIS**

**Definition**

A systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk.

Primary osteoporosis is defined as osteoporosis that occurs in an individual who has no endocrinopathy or other disease state that would account for the changes in bone mass.

This is further classified on the basis of the patterns of bone loss and fracture.

Type I (post-menopausal) or osteoclast-mediated osteoporosis is characterized by rapid bone loss occurring in the post-menopausal period and is consistent with high bone turnover osteoporosis. There is a rapid phase of bone loss predominantly involving trabecular bone and an association with vertebral and distal radial fractures.

Type II (senile) or osteoblast-mediated osteoporosis is related to aging, chronic calcium deficiency, increased parathyroid hormone activity and decreased bone formation.

Both types may be seen in the same individual over time.
**Peak Bone Mass**

Most studies indicate that peak bone mass is attained by the 20th year. Blacks have a higher bone density than whites.

Bone mass is lower in daughters of osteoporotic mothers but the effect is not invariably found.

Delayed puberty leads to a smaller peak bone mass, Malnutrition, high altitude and excessive childhood exercise delay the menarche.

Daily calcium intake in children is controversial. There is no compelling evidence to suggest that on a mixed diet, calcium plays a critical role in the attainment of peak bone mass. Vitamin D 400IU per day and fluoride 1 ppm in the water help attain a better peak bone mass.

Exercise is an important determinant of peak bone mass. Lack of physical activity is a risk factor for osteoporosis.

Bone loss probably starts in the late 30’s which might coincide with decreased physical activity.

**Determinants of fracture**

The size of bone does not decrease with age but rather the porosity increases. This is described as a decrease in bone mass or a decrease in bone mineral density (BMD). This BMD is the peak bone mass that the person attained at age 20 years minus the amount of bone lost with time or through disease. Bone mass is not the sole determinant of fracture risk. The tendency for elderly people to fall more easily is a contributory factor.

BMD accounts for the difference in fracture risk between men and women. Women have a lower peak BMD and have a greater age-related bone loss.
The rate of bone loss in healthy men, and probably premenopausal woman, is low and calculated at about 3-5% per decade. The view that considerable bone is lost before the menopause has not been substantiated in prospective studies.

The rate of bone loss in the first 10 years postmenopausal varies considerably between women from a low of 1% per year (slow bone loosers) to a high of 5% per year (fast bone loosers).

**Other Fracture Risks**

A long femoral neck correlates with an increased risk of fracture.

Falling: a fracture is 13 times more likely if the point of impact is directly over the trochanter. Padding over the hip (fat or an artificial cushion) reduces the risk.

Women lose 2-4% per annum in the first 5-10 years after menopause

**The Diagnosis of Osteoporosis:**

Using BMD the WHO criteria for osteoporosis are:

1. Normal. A BMD value of not more than 1 standard deviation (SD) below the average of young adults
2. Low bone mass (osteopenia). A BMD value of more than ISD below the young adult average but not more than 2.5SD below
3. Osteoporosis. A BMD value of more than 2.5 SD below the young adult value.
4. Severe osteoporosis. A BMD more than 2.5 SD below and the presence of one or more fragility fractures. In men a criteria of 3SD should be used.

Using these criteria about 30% of postmenopausal women measured at the spine, hip and forearm, are osteoporotic. Measurements made at one site alone give a prevalence of 15-20% which is about the lifetime risk of a single osteoporotic fracture at that site. Fractures below the age of 75 years occur mainly in women and affect the wrist and spine. Hip fractures occur later in life, that is above 75 years, and then in both men and women.
Clinical Indications for Bone Densitometry

A. Presence of strong risk factors:
   1. premature menopause (< 45 years)
   2. prolonged secondary amenorrhoea
   3. primary hypogonadism
   4. corticosteroid therapy (< 7.5mg for > one year)
   5. anorexia nervosa
   6. malabsorption
   7. primary hyperparathyroidism
   8. hyperthyroidism
   9. prolonged immobilisation

B. Radiological evidence of osteopenia or vertebral deformity

C. Previous fragility fracture

D. Monitoring therapy

Hip Fracture

Mortality from a hip fracture is high (12-40%).

Multiple risk factors contribute to the risk of hip fractures. Low bone mineral density is obviously important but the following all increase the risk independent of the BMD:

- se of benzodiazepines-increased risk of falling
- aternal history of a hip fracture
- se of anticonvulsants
- ack of exercise: aim for at least 4 hours per day on the legs (standing and walking)
- physical weakness: measured as an inability to rise from a chair without the use of the arms.
- ecent loss of body weiht
- xcess caffeine use: this increases urinary loss of calcium.
- lcohol abuse.
Hip fractures typically occur when falling from the standing position. The use of padded hip protectors in institutions has reduced the incidence of hip fractures.

**Vertebral Fracture**

These are classified as central, crush or wedge fractures. Fractures occur often spontaneously or from minimal trauma e.g. coughing or lifting. The midthoracic and thoroco-lumbar vertebrae are most involved. Multiple fractures occur in about half the cases. These fractures may be asymptomatic or minimally symptomatic.

There is an exponential increase in the incidence with age. Very little is known about osteoporotic vertebral fractures in men. The limited data available indicate the incidence to be about half that of women. The consequences of these fractures are back pain, kyphosis and loss of height. From the limited data available, it would seem that about half the fractures are symptomatic. New crush fractures can give rise to acute back pain but may also be of gradual onset. The pain is usually well localised and is relieved by bed rest. Pain decreases over a period of weeks to months but some have chronic pain and disability. Still others have no pain and lose of height is the only indication of the disease. After the first fracture, 85% will have recurrent fractures and 75% will lose 10cm in height over the next 10 years.

**Forearm Fractures**

They are usually caused by a fall on the outstretched hand. The incidence increases rapidly in women from the first 5 years postmenopause to peak between 60 and 70 years.

**STRATEGIES FOR PREVENTION:**

1. Population based to raise the BMD to decrease the risk of fragility fractures.
   These would include:
   - higher levels of exercise
   - stop smoking
   - a high calcium diet
   - universal usage of HRT in postmenopausal women.
2. Patients at particular risk are:
   - women with low bone density
   - patients likely to fall
   - certain diseases

Some of these are difficult to implement so the major thrust has been directed towards preventing bone loss that occurs in association with the menopause.

OPTIMAL CALCIUM INTAKE

Normal absorption of calcium by the gut requires an acidic gastric Ph, adequate serum levels of 1,25- dihydroxyvitamin D and an appropriate calciumphosphate ratio. Inhibitors of gut calcium absorption include low vitamin D levels, high dietary phosphates (soft drinks), fat, phytates and oxylates, achlorhydria and sprue. Drugs that inhibit calcium absorption include phenytoin, isoniazid, corticosteroids, heparin, tetracylines and furosemide.

Calcium insufficiency is regarded by many as a salient risk factor. Several studies have shown that calcium (over lgm of elemental calcium per day) is capable of slowing the rate of bone loss in women after the menopause, with or without osteoporotic fractures. The rate of bone loss may be halved, at least in cortical bone but certainly in cancellous bone as well. It seems likely that the mechanism is a slight increase in serum calcium which suppresses PTH secretion. Calcium plus Vit. D has a even better protective effect of the rate of hip fracture.

Optimal intake in children must be made bearing in mind that much of the worlds population has an intake of under 400mg/day. Black children in the US have a similar low intake with little evidence of osteoporosis in their adult years. Despite this an adequate to above adequate calcium intake results in a higher peak bone mass. Optimum calcium requirements recommended by the United States National Institutes of Health Consensus Panel are:
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<tr>
<td>Adolescents</td>
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<td>Men 25—65 years</td>
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<td>1500</td>
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HORMONE REPLACEMENT THERAPY (HRT)

On adequate doses of HRT, further bone loss is completely stopped in about 80% of women, but 20% will continue losing.

Numerous studies show that HRT consistently reduces the risk of hip and forearm fractures. A major uncertainty is whether the effects of HRT persist or whether catch-up bone loss occurs after several years. Some observational studies have suggested that the effects of oestrogen, e.g. on hip fracture, are less in elderly (over 75 years) women, that at the time of the menopause. It has been argued that when estrogens are stopped, catch-up bone loss occurs so that 10-20 years or so thereafter, bone mass in treated patients would be the same as in untreated controls. However recent prospective studies suggest that oestrogen withdrawal does not result in catch-up loss of bone, at least for up to 7 years after stopping treatment. The view that the effects of HRT may wear off sometime later is supported by other observations. Thus, 10 years of HRT at the menopause would have a progressively decreasing impact on hip fracture after the age of 70 years, when most of the burden falls in elderly communities.
CORONARY HEART DISEASE

HRT consistently reduces the risk of CHD by 30-50% also has a favourable influence on the blood lipid levels and is dose responsive. Progesterone has a slight negative effect on the serum lipids, reducing the positive effects of oestrogen by a third. The newer synthetic progestogens may well have less of a negative effect on lipids.

ENDOMETRIAL CANCER

Long-term unopposed oestrogen therapy increases the risk of endometrial cancer. The effect is dose dependent and the risk increases with increasing duration of oestrogen use. The addition of a progesterone to the oestrogen regimen prevents this increase.

BREAST CANCER

The view that oestrogen therapy is associated with an increased risk of breast cancer is plausible. Numerous studies have been conducted with conflicting results. One meta-analysis has shown that 15 years of oestrogen therapy will increase breast by 15%. After 10 years from the menopause of uninterrupted use the relative risk of breast cancer is 1.46. The use of ostrogens for 5 to 7 years in older women (60 to 65 years) seems to be associated with an even higher relative risk of 1.71. Adding progesterone does not reduce the risk of breast cancer. Most publications see benefits of oestrogen therapy to outweigh the perceived disadvantages.

COMPLIANCE

The main problem with HRT is the reluctance of women to take it and to take it for sufficient periods of time to have a significant effect on fracture risk. About 10% of post-menopausal women take HRT but the compliance after 12 months is only about 50%. Side effects of the HRT including increased body weight, breast tenderness and vaginal bleeding are major reasons for stopping therapy.
EXCERCISE AND PHYSICAL ACTIVITY

Physical activity is an important but incompletely understood factor in bone formation. Impact-loading exercises appear to be effective but site-specific in the maintenance of bone mass. Numerous conflicting studies would seem to indicate a definite place for load bearing exercise in the prevention of osteoporosis. Unfitness from lack of exercise is a separate risk for fracture because of an increased risk of falling. A target of 4 hours per day on the legs, either walking, standing etc. has been advocated, particularly in the elderly.

As a group, women who exercise and maintain normal menstrual cycles have the greatest bone mass. Eumenorrheic women who do not exercise have less bone and amenorrheic women who exercise have the least bone. The etiology of the amenorrhea is inadequate caloric intake and the amenorrhea will not respond to hormone therapy unless the calory intake is increased. The constellation of disordered eating, amenorrhea and osteoporosis (often presenting as stress fractures) is recognised as a serious threat to the health of the female athlete.

CALCITROPIC HORMONES

Vitamin D

Vitamin D directly affects bone metabolism by playing a critical role in calcium metabolism. It actively increases absorption of calcium by maturing the villus lining cells of the intestine and stimulating them to produce calcium-binding protein. Small doses of vitamin D (400 units per day) are indicated in osteoporotic patients.

The calcitonins

Calcitonin responds to elevated serum ionic calcium levels by decreasing the number and activity of osteoclasts and functions as an inhibitor of bone resorption and thereby decreases plasma calcium and the urinary excretion of hydroxyproline. It also functions as a neuropeptide with strong analgesic effects.
In the early phase of treatment when resorption is blocked but formation from old BMU is active, skeletal mass will improve but this will taper off when the new steady state has been achieved.

The usual dose is 100IU SCT calcitonin IMI daily to 3 times a week. Calcitonin can be used for acute bone pain of recent fractures the effect of which is apparent 1-2 days after the start of treatment. Analgesic dosages are 100IU units 3 times a week. Side effects are frequent but inconvenient rather than serious. In 30% nausea occurs. Other symptoms include flushing, vomiting, diarrhoea. In general calcitonin appears to be remarkably safe.

BISPHOSPHONATES

They are analogues of pyrophosphate. The major effects of the bisphosphonates is inhibition of osteoclastmediated bone resorption. If given in high enough dosages they inhibit the mineralization of cartilage and bone and are used to suppress heterotopic calcification following hip surgery.

Very little is known about the nature of the effect of the bisphosphonates on bone resorption but the end result is to decrease the functional performance of the osteoclasts. The activation of new modelling sites is reduced and the depth of the excavations is reduced.

The bisphosphonates are poorly absorbed from the GIT. Only 1-5% is absorbed but this is reduced to near zero in the presence of calcium containing foods or other divalent ions which chelate the bisphosphonates. Thus they must be taken on an empty stomach.

Bisphosphonates are rapidly taken up by the skeleton. Uptake is considerably increased in focal disorders such as Pagets disease and metastatic bone disease. The half life of the bisphosphonates is extremely long, perhaps as long as 7 years and is related to the turnover time of the skeleton.
All bisphosphonates have been shown to suppress bone loss in postmenopausal osteoporosis as well as in several forms of secondary osteoporosis e.g. steroid induced. Further sustained increases in bone density in women on alendronate is evident over 3 years which is surprising for an antiresorption agent. This suggests some reversal of osteoporosis might be possible over a longer period.

New fracture rates in women on bisphosphonates are about halved and is particularly noticed in the older group (65 years and over) as well as a trend towards reduction in non-vertebral fractures.

The bisphosphonates reduce the bone pain of metastatic bone disease but no trials have been done for fracture pain.

Side effects are few. Intestinal intolerance occurs in a small percentage of cases and oesophageal erosions have been reported with alendronate and pamidronate. As a result the tablets should be taken after arising in the morning on an empty stomach but with a full glass of water to ensure the tablet passes through the oesophagus.

FLUORIDES

Fluoride is a trace element with a particular affinity for bone. It is one of the few agents with a marked anabolic effect on bone. It is rapidly absorbed by simple diffusion but the bioavailability is significantly reduced by food, calcium and antacids. Sodium fluoride promotes recruitment of active, normal osteoblasts independent of any coupling between bone resorption and formation. This new bone formed is histologically not entirely normal. The bone matrix is irregularly fibrous rather than lamellar. Mineralisation can also be defective resulting in generalised or focal osteomalacia unless there is adequate calcium intake with fluoride therapy.

Histological studies show than cancellous bone increases markedly. The mean thickness of new bone formed is increased. Effects on cancellous bone in the spine are dramatic in about 60% of cases with bone mineral mass increasing to near normal, within 5 years. In 40% there is no increase. There is little evidence that fluoride increases bone mass at cortical sites.
In contrast to the antiresopptive drugs already described, fluoride causes osteoblast proliferation and stimulates new bone formation. Sodium fluoride has been repeatedly and reproducibly shown to increase bone mass in a dose-dependent manner. Despite this the ability of fluoride to reduce the vertebral fracture rate in established osteoporosis has been controversial. Early trials showed a possible increase in fracture rate despite the increase in the amount of new bone. These trials involved high doses of fluoride. During high dose fluoride therapy a calcium deficiency may occur due to the increased mineralisation of the new bone. This renders the patient vulnerable to secondary hyperparathyroidism. Vitamin D supplementation with calcium corrects this effect. Better results are possible with lower doses of fluoride (50mg/day) in a delayed release form. A complex relationship exists between the rate of new bone formation, serum fluoride levels and the fracture rate. It now seems that fluoride therapy decreases the rate of vertebral fractures as long as bone production proceeds slowly enough to allow for proper mineralisation and as long as the fluoride levels do not exceed a toxic threshold. The ideal role of fluoride in the future may be to augment bone density in the early stages of therapy and then switch to antiresorptive agents for the long-term maintenance of bone density.

Side effects are mainly gastrointestinal. This is a chemical gastritis from hydrofluoric acid. The newer slow release preparations should prevent this. Acute pain, tenderness and swelling mainly in the heels and ankles is well described. The pain is disabling and therapy must be stopped immediately. It completely recovers in 6-8 weeks. It is cause by a stress fracture through an area of excessive osteoid formation but which has not yet mineralised. The fear is if this occurs at a site such as the hip in might lead to a true fracture. Some bone pain might be due to microfractures which concentrate the fluoride and slow the healing process.

TESTOSTERONE AND THE ANABOLIC STEROIDS

Testosterone has marked positive skeletal balance effect. The masculinizing effects are unacceptable to women.

The main indication for the use of testosterone is in male osteoporosis with proven hypogonadism.
Anabolic steroids include an early and marked decrease in urinary calcium excretion. It is believed that the anabolic steroids stimulate bone formation, decrease bone resorption or both. Serum bone markers do not change much.

The mechanism of action is unknown but it is believed that they work through androgen receptors and stimulate osteoblast-like cells. The number of osteoclasts is also stimulated thus all elements of remodelling in cancellous bone are involved but in favour of the osteoblast. The increment in wall thickness is marked (18%) and comparable to that of fluoride. There is no clear cut evidence that the anabolic steroids reduce fracture rate but it is believed to be effective.

Other effects is a marked reduction in fat and an increase in lean body mass. Another important effect is on lean muscle mass and muscle strength which increases. Use of anabolic steroids have been shown to reduce the risk of falling in the elderly. Side effects are well known. Hepatic transaminases increase in 50% of cases and the induction of an atherogenic lipid profile. For this reason they are only used in the aged. Sodium retention can also be a problem.

Clinical use is in the frail and the elderly is indicated.

OSTEOPOROSIS IN THE MALE

Osteoporosis in the male has been much less studied than in the female. A thorough evaluation of osteoporosis in the male is warranted because definable pathogenetic factors are seen in many cases.

Peak bone mass is higher in men than women and as can be expected osteoporosis is much more prevalent in women but up to one third of hip fractures are in men. Vertebral fracture, the most common fracture in women are unusual in males under 70 years.
Base line investigations in male osteoporosis should include:
- urea and electrolytes
- serum glucose
- liver functions
- thyroid functions
- FBC and ESR
- testosterone, sex hormone binding globulin, FSH, LH.
- serum and urine electrophoresis
- prostate specific antigen
- 24 hour urinary calcium excretion

A continuous positive relation exists between physical activity and bone mass in healthy white males. The histological findings are comparable to those found in oestrogen deficiency in women and include the disruption of skeletal architecture.

Six groups of aetiologies of male osteoporosis have been proposed:

1. Changes in the general state of health and toxic causes.
   Prolonge immobilization, nephrolithiasis, gastrectomy, malnutrition, chronic hepatitis, chronic renal diseases, inflammatory diseases and diabetes Alkohol Tobacco.
2. Drug-induced bone loss.
   Long-term glucocorticoid therapy, excessive thyroid hormone replacement, chronic heparin therapy, anticonvulsants and phenobarbital use.
3. Renal causes.
   Idiopathic renal hypercalciuria
4. Hormonal causes
   Testosterone deficiency
   Hypergonadotropic hypogonadism
   Hypercorticism
   Hyperthyroidism (often mild)
5. Unusual causes
   Haemchromatosis
   Sarcoidosis
Gaucher’s disease
Hypophosphatasia
Haemoglobinopathies

Alcohol is a significant risk factor for osteoporosis in both men and women, but alcohol abuse is more common amongst men. Alcohol abuse remains one of the main causes of male osteoporosis.

Hypogonadism is also a major cause of male osteoporosis. Serum testosterone levels should always be measured.

Hypercalcemia in the male is more common than many realise. A 24 hour urinary calcium determination should always be done.

Very little is known about osteoporotic vertebral fractures in men. The limited data available indicate the incidence at about half that of women and unusual under the age of 70 years. Never-the-less many elderly men have a slowly evolving dorsal kyphosis with chronic back pain in this area. Osteoporosis should be considered in these cases. The wedge shaped vertebrae of Schuermannnn’s disease and degenerative spondylitis must not be confused with the wedging of osteoporosis. The radiological picture can be very similar.

**Androgen therapy in Men**

Androgen therapy is indicated in hypogonadal men. Treatment with 200-300mg IMI every 2-3 weeks is given. Oral esterified testosterone can also be given by mouth in a 60mg BD dosage. The most serious complications is peliosis hepats (blood filled cystic lesions) and hepatoma but are rare on replacement dosage. Care should be taken in patients with prostatic hypertrophy and not used in prostatic cancer.