**Aims and Objectives**

To identify, define and examine a range of diseases that are a consequence of altered bone formation or resorption—specifically:

- Osteoporosis
- Paget’s
- Osteopetrosis
- Metastatic bone disease
- Osteogenesis Imperfecta
- Fibrodysplasia ossificans Progressiva
Metabolic Bone Diseases - altered osteoclastic function

- Osteoporosis
- Paget’s
- Osteopetrosis
- Metastatic Bone Disease
Metabolic Bone Diseases - altered osteoblast function

- Osteogenesis Imperfecta
- Fibrodysplasia Ossificans Progressiva - FOP
Osteoporosis

Systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue – bone fragility and susceptibility to fracture
Osteoporosis

Resorption exceeds formation

normal

Developing osteopaenia
Normal strut → thinning → break in connectivity

Fast resorption of strut → Irreplaceable loss of connectivity
Thinning of vertebral bone with osteoporosis
Osteoporosis

Who is at risk

PM women – 1 in 4 will have vertebral fracture by the age of 60

- 1 in 12 men – 30% hip fractures
- Men and women over 75 (senile osteoporosis)

Vertebral crush fracture
Top of spine
Osteoporosis

Statistics
60,000 Hip, 50,000 forearm and 40,000 vertebral fractures

Cost - £640million
Healthcare O and R £970million
Other Fractures: 300,000+

Vertebral Fractures: 500,000+

Hip Fractures: 300,000+

Wrist Fractures: 200,000+
Osteoporosis

Risk factors

Endogenous
- Age
- Female
- Asian/Caucasian
- Family History

Exogenous
- GC therapy
- Primary HPT
- Cigarettes,
  Alcohol

Trabeculae microfracture
Surrounding callus
Osteoporosis

Treatment - Strategies
- Lifestyle – diet, alcohol, exercise, smoking
- Genetic and BMD studies
- HRT, CT, BPs
- Int PTH (1-34)

Compression fracture and
Loss of trabeculae bone
Osteoporosis - Genetics

50 - 85% variance in BMD at skeletal sites is genetically determined

Twin studies – Hip axis length, BMI, muscle strength, age at menarche/menopause all have a genetic component
Paget’s Disease
Paget’s Disease

Common chronic bone disease characterised by excessive osteoclast activity and bone formation

- Primary abnormality – osteoclast
- ? RNA paramyxovirus role
- Resorption followed by new bone formation

Tibial bowing
Paget’s Disease

- osteoclasts
- nos increased 100 fold
- Multinuclearity observed
- ? Stimulus activation
- 3x ocl – activity unchanged
Paget’s Disease

Destruction and overgrowth of trabecular plate

Pagetic skull – cotton wool appearance
Paget’s Disease

Who is at risk?

Geographic – GB, USA, NZ and Australia – Lancashire 6.3-8.3% of people over 55 have Paget’s

Genetic – 15-30% patients have +ve family history

Ethnic – Anglo-Saxon – European – rare in Asians
Paget’s Disease

SYMPTOMS
- Bone pain,
- Deformity
- Fracture,
- Compression of nerves

Normal and Pagetic articular surfaces
Thin cartilage/irregular subchondral bone
Paget’s Disease

- Develop after 40 y.o.a
- Monostotic or polystotic
- Sites – Pelvis, femur, spine, skull, tibia
Paget’s Disease

Treatment – block bone resorption

- Inhibition of Pagetic osteoclasts
- Bisphosphonates
  - alendronate, risedronate, pamidronate, etidronate
- Calcitonin
Osteopetrosis
Osteopetrosis

Rare disorder characterised by marked increased density of skeleton

Two forms:
- **Autosomal recessive** – **infantile** – malignant – lethal in utero/childhood
- **Autosomal dominant** – **adult** - benign

Increased density in all bones
Osteopetrosis

Abnormality

- Failure of osteoclastic resorption
- Woven bone often present
- Osteoclasts may be present, or few - lack ruffled borders
- Calcified cartilage

Adult - increased density - thumbs
Osteopetrosis

**Clinical**
- Increased bone mass – X-ray
- Cortical bone thickened
- Skull thickened and dense
- Long bones brittle/fracture
- Diaphyses/metaphyses broadened
- Patients asymptomatic
Osteopetrosis

**Adult form – Albers-Schonberg**

- Thickening of skull
- Thickening of vertebrae
Osteopetrosis

**Treatment**
- Bone marrow transplantation – infantile op
- Calcium deficient diet
- Vitamin D3

To stimulate bone resorption
Metastatic Bone Disease

Osteolysis or bone formation as a consequence of tumour cell metastasis to bone.

**Primary solid tumours**
Breast, Prostate, lung

**Soft tumours** – myeloma
80% present with bone pain
Metastatic Bone Disease

- Bone Pain
- Hypercalcaemia
- Fracture

30-50% of all tumours metastasise to bone
Skeletal metastasis affect 65-75% patients

Osteolytic lesion – femur - Breast cancer patient
Metastatic Bone Disease

**Osteolysis** – increased resorption – breast cancer
or **osteosclerosis** – Prostate cancer

Metastases to axial skeleton
vertebrae, pelvis, skull, longbones

Pancreatic tumour
Woven bone formation
Sclerotic lesion
Metastatic Bone Disease

- Migration, adhesion
- Proliferation and growth factor production
- Osteoclastic/osteoblastic activity
Metastatic Bone Disease

**Clinical presentation**
- Hypercalcaemia (advanced bone destruction)
- Intractable bone pain
- Pathologic fracture after trivial injury
- Nerve compression (spinal)
Metastatic Bone Disease

Tumour induced bone resorption

Key factor – Parathyroid hormone related protein

Treatment

- Bisphosphonates – myeloma and breast cancer
- Glucocorticoids
Osteogenesis Imperfecta

O.I – Brittle bone disease – due to defects in TYPE I collagen

Disorder of connective tissue – Types I- VII
Mainly I-IV

Type I – Mild, osteopaenia, blue sclera, prepubertal fracture

Type II – Lethal perinatal form

Type III – Progressively deforming bones, short stature, D.I

Type IV – Normal sclerae, bone deformity, hearing loss
Osteogenesis Imperfecta

Type III and IV recurrent fractures
Major NHS burden

Limited mobility, scoliosis
I in 6,000 affected
200 Children with type III

Anterior bowing of tibia
Short stature
Osteogenesis Imperfecta

**Clinical**
- Osteopaenia, fracture, deformity
- Growth plates affected - fragmented and irregular
- Osteoclasts appear normal
- Bone tissue devoid of trabecular pattern

Disrupted growth plate
Nodules of cartilage
Osteogenesis Imperfecta

Collagen Defects
Type I – Reduced amounts
Type II, III, IV – Structural defects
(Glycine substitution in Gly-Pro-Hydroxy-Proline)

OI with osteoporosis
Osteogenesis Imperfecta

Osteopaenia due to OI

Fracture

Disuse osteoporosis

Treatment by immobilisation
Osteogenesis Imperfecta

Treatment - Cyclical Pamidronate therapy

Reduce bone pain, improved motor function, BMD increased, bone resorption decreased
Fibrodysplasia Ossificans Progressiva
Fibrodysplasia Ossificans Progressiva

A rare genetic condition resulting in bone Formation in soft tissues

- Dominantly inherited - 1 in 2 million
- Defect in skeletal patterning
  Especially big toes are associated with bone formation (Hallux deformity)
Fibrodysplasia Ossificans Progressiva

Clinical presentation

Heterotopic ossification
Fibrodysplasia Ossificans Progressiva

Clinical presentation

Heterotopic ossification
Fibrodysplasia Ossificans Progressiva

Clinical presentation

Hallux Deformity
Defect in skeletal patterning
Fibrodysplasia Ossificans Progressiva

Abnormality
Ectopic ossification – paraspinal muscles
Proximal to distal sites

Mutation in BMP family
- Role for noggin (inhibitor of BMP)

Heterotopic ossification
Fibrodysplasia Ossificans Progressiva

Ossification around shoulder joints and paravertebral area

Treatment

- None beneficial
- Failure of diagnosis leads to biopsy - bone formation - catastrophic

Surgery(!) GC, BPs, Radiotherapy

Tumour – Rhabdomyosarcoma

Ossification around shoulder
Joints and paravertebral area
Metabolic Bone Diseases

SUMMARY

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