Skeletal

Bone function

Bone function

Bone roles in the body[1]

The bony skeleton is a remarkable organ that serves either a structural function to provide mobility, support, and protection for the body or a reservoir function, as a storehouse for essential minerals. It is not a static organ, but it is continuously changing. The architecture of the skeleton is adapted to provide adequate strength and mobility.

The skeleton is a storehouse for two minerals, calcium and phosphorus, that are essential for the functioning of other body systems. The maintenance of a constant levels and as well as an adequate supply of calcium and phosphorus in cells is critical for the function of all body organs, particularly for the nerves and muscle. Therefore, a complex system of regulatory hormones has developed to maintain adequate supplies of these minerals. These hormones act not only on bone but on other tissues, such as the intestine and the kidney.

As the skeleton is simultaneously serving two different functions that are in competition with each other, it is difficult to maintain bone heath. First, bone must be responsive to changes in mechanical loading or weight bearing to have sufficient supplies of calcium and phosphorus. On the other hand, when these elements are in short supply the regulating hormones take them out of the bone to serve vital functions in other systems of the body. Thus the skeleton can serves as a bank where we can deposit calcium or phosphorus and then withdraw them later in times of need. However, too many withdrawals weaken the bone and can lead to the most common bone disorder, fractures.

Very important part of bone, but out of scope of this material is its interior part: bone marrow. This is the flexible tissue which produces several types of cells:

- Hematopoietic stem cells give rise to the three classes of blood cells that are found in the circulation: leukocytes, erythrocytes, thrombocytes.
- Mesenchymal stem cells are found arrayed around the central sinus in the bone marrow. They have the capability to differentiate into osteoblasts, chondrocytes, myocytes, and many other types of cells.
- Endothelial stem cells.

Bone structure

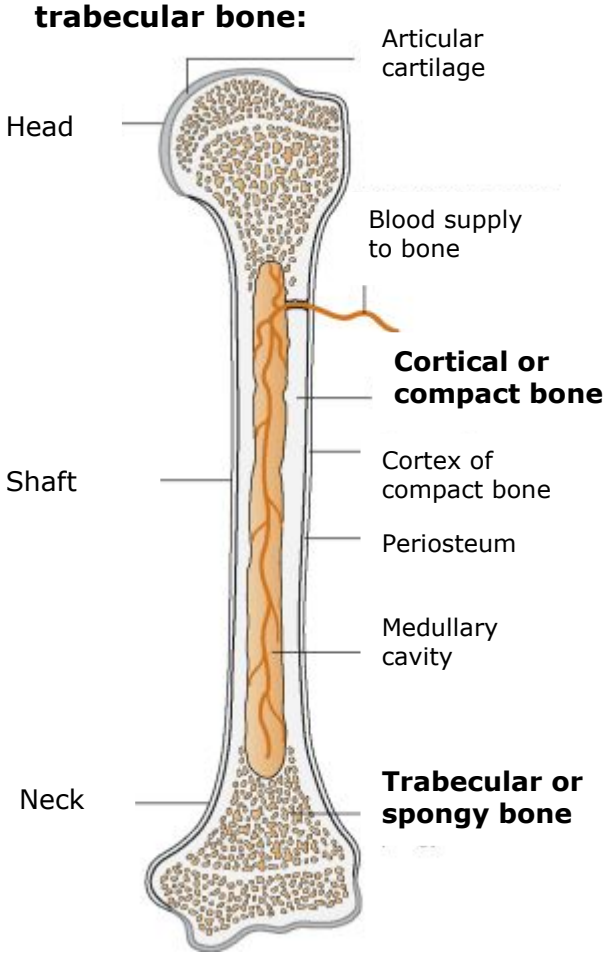
Bone is a composite material, consisting of crystals of mineral bound to protein. This provides both strength and resilience so that the skeleton can absorb impact without breaking. A structure made only of mineral would be more brittle and break more easily, while a structure made only of protein would be soft and bend too easily. The mineral phase of bone consists of small crystals containing calcium and phosphate, called hydroxyapatite. This mineral is bound to a matrix that is made up largely of a single protein, collagen. Collagen is made by bone cells and assembled as long thin rods containing three intertwined protein chains, which are then assembled into larger fibers that are strengthened by chemical connections between them. Other proteins in bone can help to strengthen the collagen matrix and to regulate its ability to bind mineral.

On the basis of bone structure, the bone is generally classified into two types:

CORTICAL BONE, also known as compact bone and
TRABECULAR BONE, also known as cancellous or spongy bone.

These two types are classified on the basis of porosity and the unit microstructure. Cortical bone is much denser with a porosity ranging between 5% and 10%. Cortical bone is primary found in the shaft of long bones and forms the outer shell around trabecular bone at the end of joints and the vertebrae. Fig.1. About 80% of the skeletal bone mass is composed of cortical bone. The other 20% is trabecular bone[2].

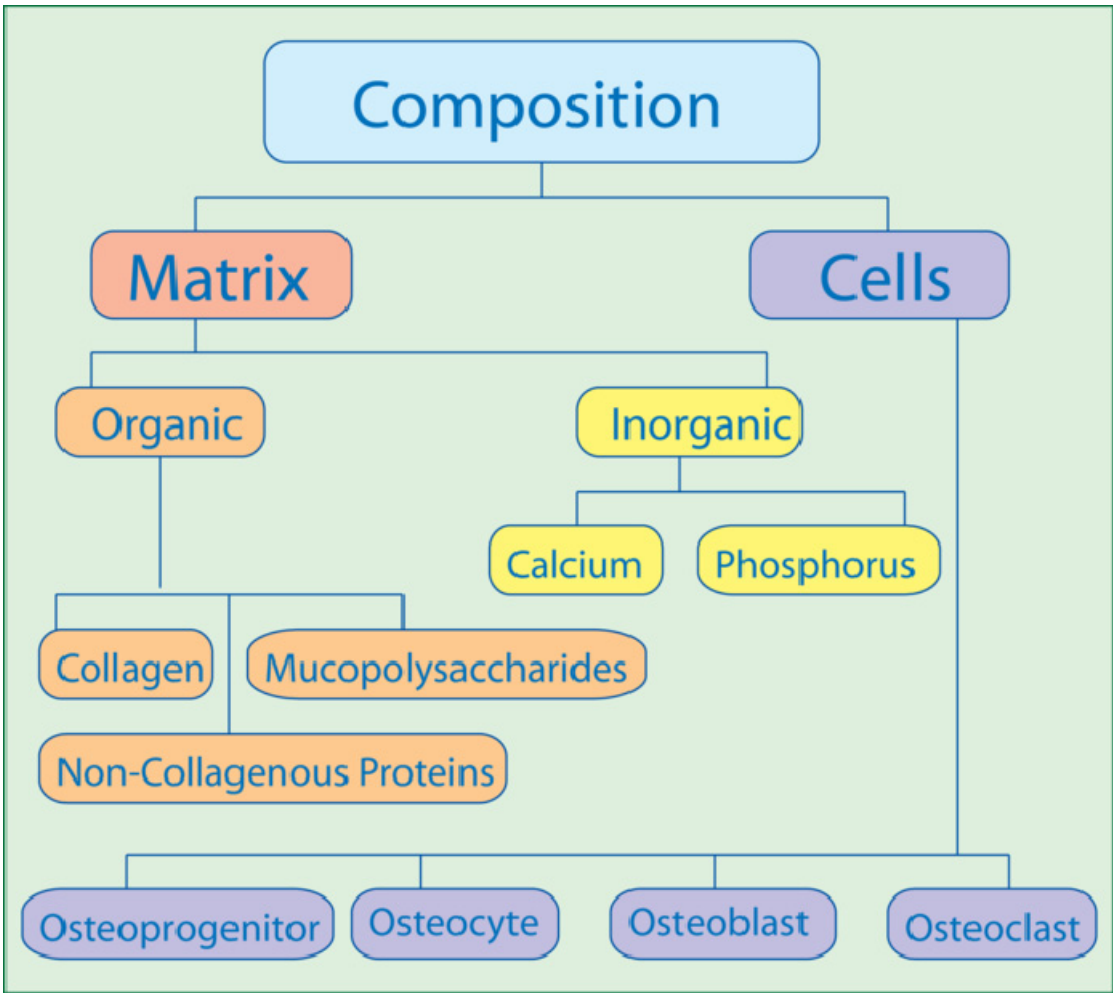
Fig.1: Cortical and trabecular bone:



Bone tissue

Bone is composed of protein, minerals and cells. The majority of bone is made of the bone matrix, which is the ground substance and in which the cells of bone exist. Bone matrix has inorganic and organic parts. The inorganic part of bone is mainly formed by crystalline of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). The organic components of matrix are collagen, mucopolysaccharides and a large non-homogenous group of non-collagenous proteins. The matrix forms the extracellular material that binds all the cellular constituents of bone together, see Fig.2.

Fig.2: Composition of bone



There are three special types of cells that are found only in the bone. These cell names all start with "OSTEO" because that is the Greek word for bone[3].

OSTEOCLASTS are large cells that dissolve the bone. They come from the bone marrow and are related to white blood cells. They are formed from two or more cells that fuse together, so the osteoclasts usually have more than one nucleus. They are found on the surface of the bone mineral next to the dissolving bone.

OSTEOBLASTS are the cells that form new bone. They also come from the bone marrow and are related to structural cells. They have only one nucleus. Osteoblasts work in teams to build bone. They produce new bone called "osteoid" which is made of bone collagen and other proteins. As osteoblasts containing large amounts of alkaline phosphatase, they also control calcium and mineral deposition. They are found on the surface of the new bone.

When the team of osteoblasts has finished filling in a cavity, the cells become flat and look like pancakes. They line the surface of the bone. These old osteoblasts are also called **LINING CELLS**. They regulate passage of calcium into and out of the bone, and they respond to hormones by making special proteins that activate the osteoclasts.

OSTEOCYTES are cells inside the bone. They also come from osteoblasts. About 10 to 20% of osteoblasts are estimated to become buried in bone matrix while the new bone is being formed, and the osteocytes then get surrounded by new bone. They are not isolated, however, because they send out long branches that connect to the other osteocytes. These cells can sense pressures or cracks in the bone and help to direct where osteoclasts will dissolve the bone.

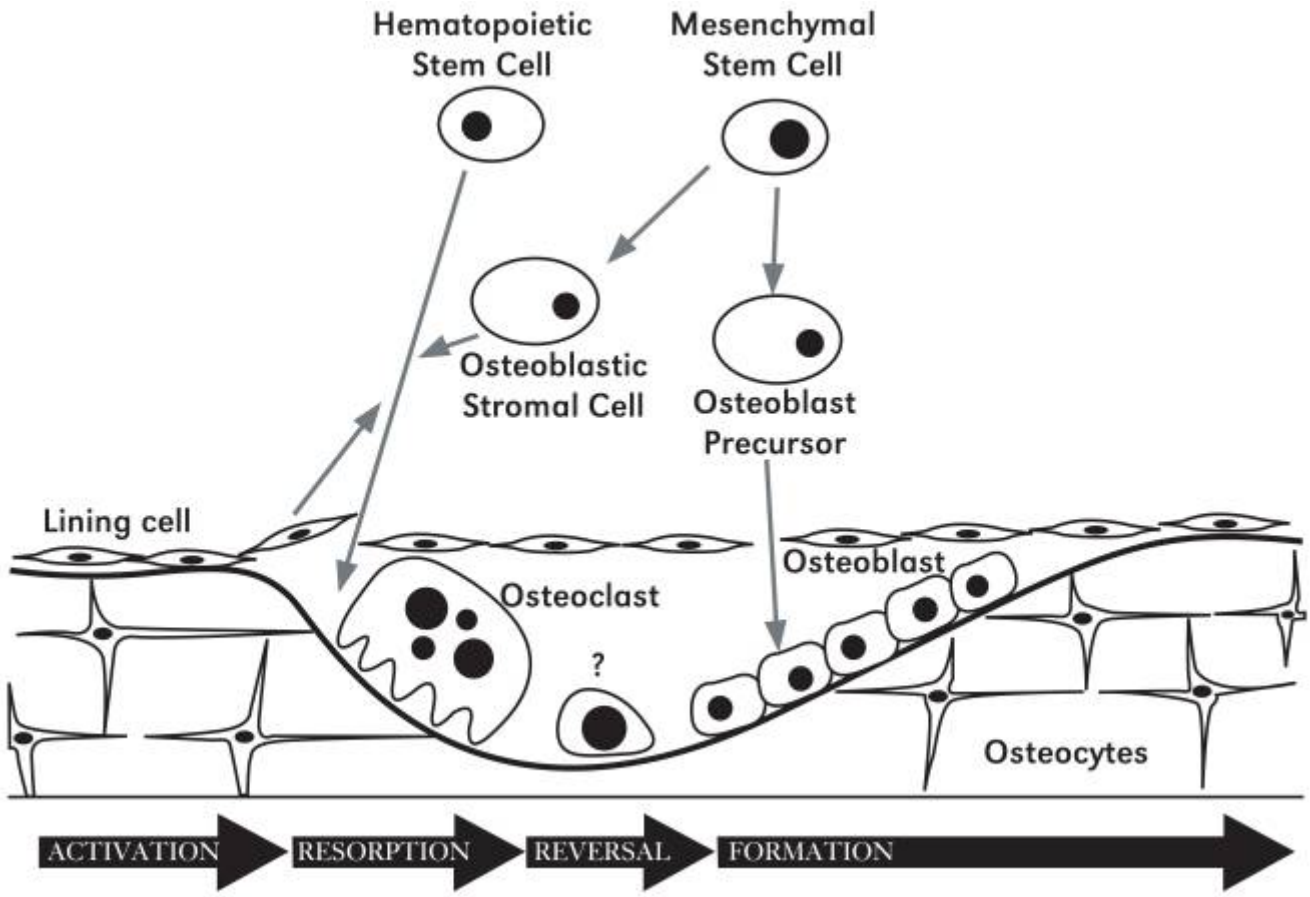
Bone metabolism

The bone tissue is metabolically active tissue, which is continuously remodeling. Bone remodeling enables bone to repair damages and adjust strength. This process is characterized by two opposite activities, the formation of new bone and the resorption (degradation) of old bone. Bone formation and resorption are interdependent processes that are, under normal circumstances, tightly coupled in time and space.

The bone remodeling cycle consists of several consecutive phases, see Fig.3:

ACTIVATION: micro-cracks of bone and consequent osteocytes signalization seem to be the main activators of bone remodeling cycle.
RESORPTION: during this phase osteoclasts digest old bone. Circulating osteoclast precursors are recruited, proliferate, and fuse to form osteoclasts. These giant multinucleated cells resorb bone and digest organic matrix. Osteoclasts seal off an area on the surface, and develop a region of intense activity in which the cell surface is highly irregular, called a ruffled border. This ruffled border contains transport molecules that transfer hydrogen ions from the cells to the bone surface where they can dissolve the mineral. In addition, several enzymes (e.g. acid phosphatase) are secreted from the ruffled border that can break down the matrix.
REVERSAL: starts when the resorbed surface is prepared for the subsequent formation phase. The mononuclear cells appear on the surface of resorption cavity and form a cement line. This thin layer of protein, rich in sugars, helps form a strong bond between the old bone and the newly formed bone.
FORMATION: stromal lining cells differentiate to osteoblasts, the mononucleate cells, which form bone by synthesizing the organic matrix, including type I collagen, and participate in the mineralization of newly formed matrix. The organic matrix of bone, i.e. young bone that has not undergone calcification, is called osteoid. The resorbed bone is completely replaced by new bone.
First three phases are relatively rapid, probably lasting only 2 to 3 weeks. The final phase of bone formation takes much longer, lasting up to 3 or 4 months.

Fig.3: The bone remodeling cycle



During the first year of life, almost 100% of the skeleton is replaced.

In adults, remodeling proceeds at about 10% of skeleton per year.

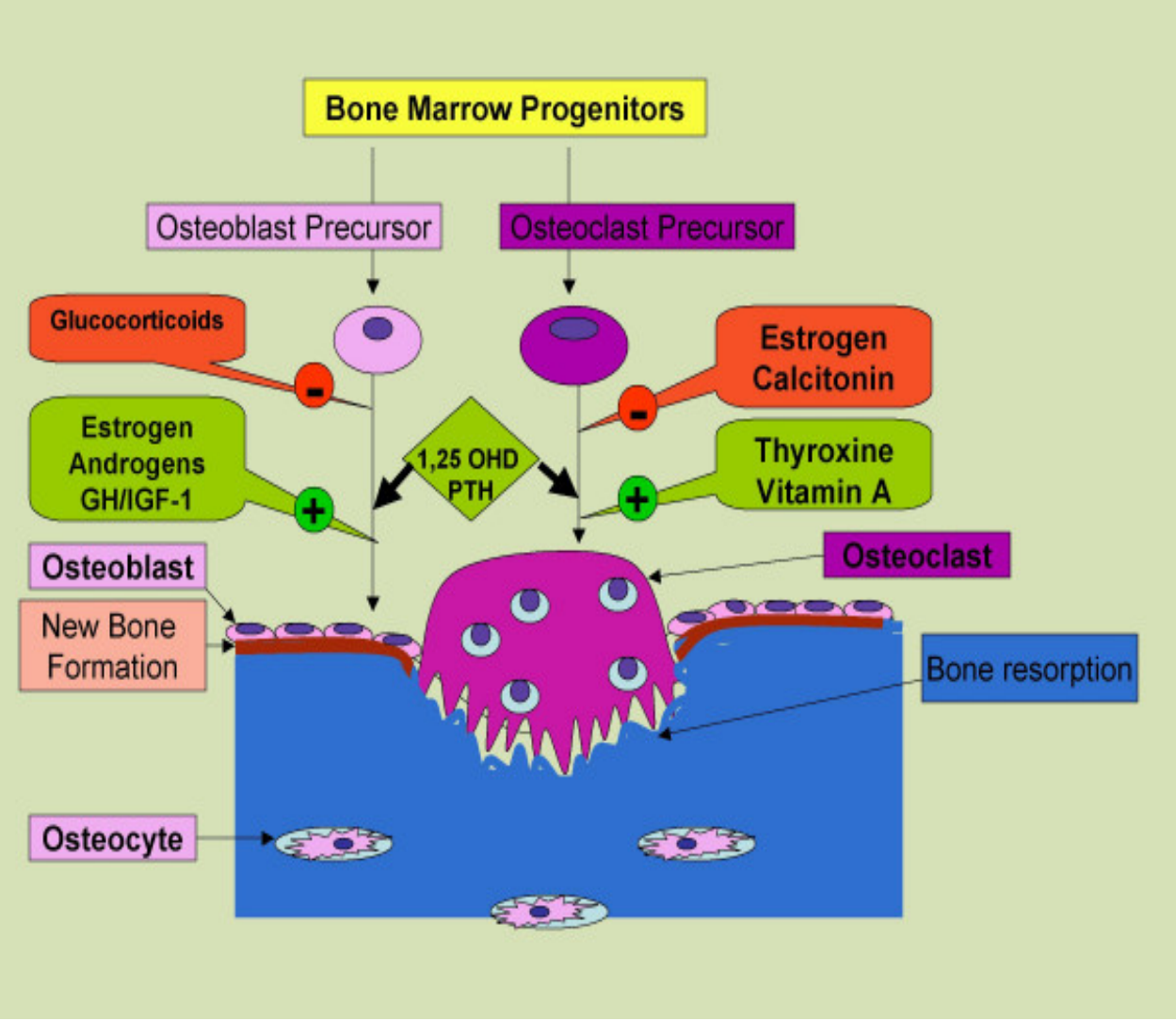
Hormones regulating bone

The growth of the skeleton, its response to mechanical forces, and its role as a mineral storehouse are all dependent on the proper functioning of a number of systemic or circulating hormones produced outside the skeleton that work in cooperation with local regulatory factors. The systemic hormones that affect the supply of calcium and phosphorus and the formation and breakdown of bone are listed in Tab.1, Fig.4. This complex system of regulatory hormones responds to changes in blood calcium and phosphorus, acting not only on bone but also on other tissues such as the intestine and the kidney.

Tab.1: The most important systemic hormones regulating bone

Calcium regulating hormone
Parathyroid hormone (PTH)
Calcitriol (also called 1,25 dihydroxy vitamin D)
Calcitonin
Sex hormones
Estrogens
Testosterone
Other systemic hormones
Growth hormone (GH)/Insulin-like growth factor (IGF-1)
Thyroid hormones
Cortisol

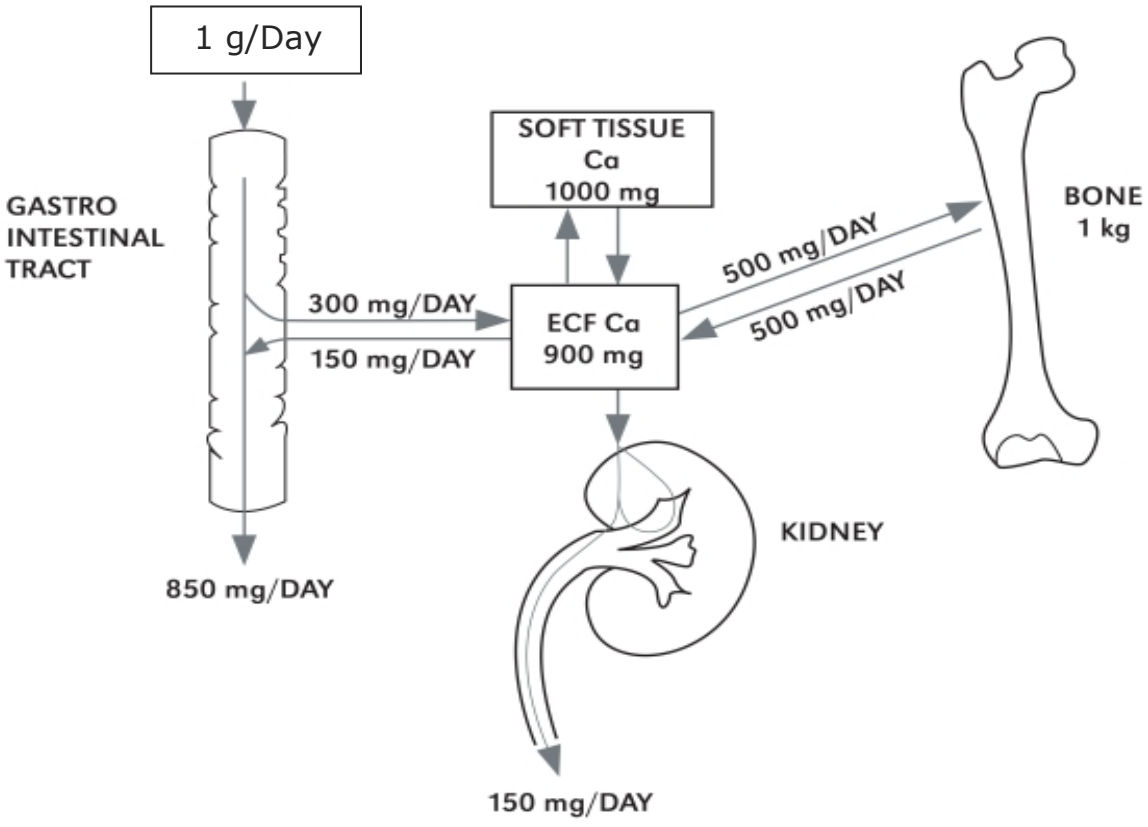
Fig.4: The most important systemic hormones regulating bone



Under normal conditions, only part of the dietary calcium is absorbed, so the net amount of calcium entering the body is only a small proportion of dietary calcium. There is equilibrium between the amount of calcium taken in and excreted in healthy young adults. The bones are constantly remodeling, and breakdown and formation are equal. The kidney filters the blood and most of calcium is taken back into the body, Fig.5. When calcium and/or phosphorus are in short supply, the regulating hormones take them out of the bone to serve vital functions in other systems of the body. Too many withdrawals can weaken the bone. The regulatory hormones, particularly PTH, and 1,25 dihydroxy vitamin D (calcitriol), also play critical roles in determining how much bone is formed.

Fig.5: Regulation of the calcium levels in the body fluids[4]

The extracellular fluid (ECF) calcium level is regulated not only by bone, but also by the intestine and kidney as shown in this figure.



Calcium-regulating hormones

Three calcium-regulating hormones play an important role in producing healthy bone:

PARATHYROID HORMONE (PTH), which maintains the level of calcium and stimulates both resorption and formation of bone

CALCITRIOL, the hormone derived from vitamin D, which stimulates the intestines to absorb enough calcium and phosphorus and also influences on bone directly

CALCITONIN, which inhibits bone breakdown and may protect against excessively high levels of calcium in the blood

Parathyroid hormone (PTH)

PTH is produced by four small parathyroid glands adjacent to the thyroid gland. These glands precisely control the level of calcium in the blood. They are sensitive to small changes in calcium concentration so that when calcium concentration decreases even slightly the secretion of PTH increases. PTH acts on the kidney to conserve calcium and to stimulate calcitriol production, which increases intestinal absorption of calcium. PTH also acts on the bone to increase movement of calcium from bone to blood. Excessive production of PTH, usually due to a small tumor of the parathyroid glands, is called hyperparathyroidism and can lead to bone loss.

A second hormone related to PTH is called parathyroid hormone-related protein (PTHrP). This hormone normally regulates cartilage and bone development in the fetus, but it can be over-produced by individuals who have certain types of cancer. PTHrP then acts like PTH, causing excessive bone breakdown and abnormally high blood calcium levels, called hypercalcemia of malignancy[5].

Calcitriol

Calcitriol, also called 1,25 dihydroxy vitamin D[6], is formed from vitamin D by enzymes in the liver and kidney. Calcitriol acts on many different tissues, but its most important action is to increase intestinal absorption of calcium and phosphorus, thus supplying minerals for the skeleton. Calcitriol also acts directly on bones where it stimulates differentiation of osteoblasts and osteoclasts. But this role does not have major physiologic importance. Vitamin D should not technically be called a vitamin, since it is not an essential food element and can

be made in the skin through the action of ultra violet light from the sun on cholesterol. Vitamin D deficiency leads to a disease of defective mineralization, called rickets in children and osteomalacia in adults. These conditions can result in bone pain, bowing and deformities of the legs, and fractures.
Treatment with vitamin D can restore calcium supplies and reduce bone loss.

Calcitonin

This hormone is produced by cells of the thyroid gland, but by different cells than those that produce thyroid hormones[7]. Calcitonin plays a role in calcium and phosphorus metabolism. In particular, calcitonin has the ability to decrease blood calcium levels by effects on two target organs bone and kidney. Calcitonin can block bone breakdown by inhibiting osteoclast and consequently inhibits the releasing of calcium and phosphorus into blood. In kidney, calcitonin inhibits tubular reabsorption of these ions. This effect may be relatively transient in adult humans. Calcitonin may be more important for maintaining bone development and normal blood calcium levels in early life. Excesses or deficiencies of calcitonin in adults do not cause problems in maintaining blood calcium concentration or the strength of the bone. However, calcitonin can be used as a drug for treating bone disease.

Sex hormones

Along with calcium-regulating hormones, sex hormones are also extremely important in regulating the growth of the skeleton and maintaining the mass and strength of bone. The female hormone estrogens and the male hormone testosterone both have effects on bone in men and women[8]. The estrogens produced in children and early in puberty stimulate bone growth. The high concentration that occurs at the end of puberty has a special effect, to stop further growth in height by closing the cartilage plates at the ends of long bones that previously had allowed the bones to grow in length.

Estrogens acts on both osteoclasts and osteoblasts to inhibit bone breakdown at all stages in life. Estrogens may also stimulate bone formation. The marked decrease in estrogens at menopause is associated with rapid bone loss. Hormone replacement therapy can be used to prevent this, but this practice can be controversial because of the risks of increased numbers of complications e.g. breast cancer, strokes, blood clots, and cardiovascular disease.

Testosterone stimulates muscle growth, which puts greater stress on the bone and thus increases bone formation. Testosterone is also a source of estrogens in the body; it is converted into estrogens in adipose cells. These estrogens are important for the bones of men as well as women. In fact, older men have higher levels of circulating estrogens than postmenopausal women do.

Other important hormones

Growth hormone (GH) is secreted from the pituitary gland and is also an important regulator of skeletal growth. It acts by stimulating the production of another hormone insulin-like growth factor-1 (IGF-1), which is produced in large amounts in the liver and released into circulation. IGF-1 is also produced locally in target tissues, particularly in bone, also under the control of GH. GH may also affect the bone directly, not only through IGF-1[9]. GH is essential for growth and it accelerates skeletal growth at puberty. Decreased production of GH and IGF-1 with age may be responsible for the inability of older individuals to form bone rapidly or to replace bone lost by resorption[10]. GH/IGF-1 system stimulates both, the osteoclast, bone-resorbing cells, and osteoblasts, bone-forming cells, but the dominant effect is on bone formation, thus resulting in an increase in bone mass.

Thyroid hormones increase the energy production of all body cells, including bone cells. They increase the rates of both bone formation and resorption. Deficiency of thyroid hormone can impair growth in children, while excessive amounts of thyroid hormone can cause too much bone breakdown and weaken the skeleton[11]. The pituitary hormone that controls the thyroid gland, thyrotropin (TSH), may also have direct effects on bone[12].

Cortisol, the major hormone of the adrenal gland, is a critical regulator of metabolism and is important to the body's ability to respond to stress and injury. It has complex effects on the skeleton[13]. Small amounts are necessary for normal bone development, but large amounts block bone growth. Synthetic forms of cortisol, called glucocorticoids, are used to treat many diseases such as asthma and arthritis. They can cause bone loss due to both decreased bone formation and increased bone breakdown, which leads to a high risk of fracture[14].

Summary of the factors regulating and influencing bone mass and strength:

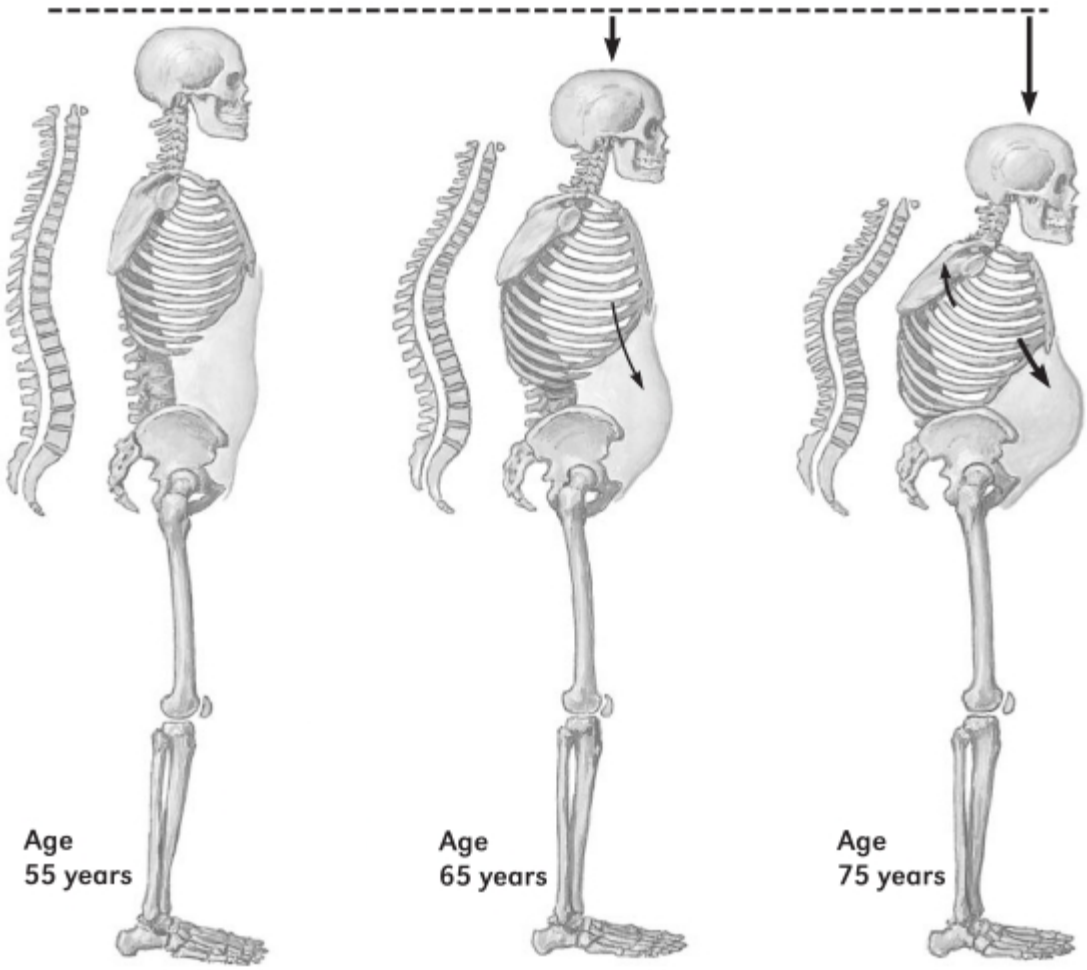
Tab.2:

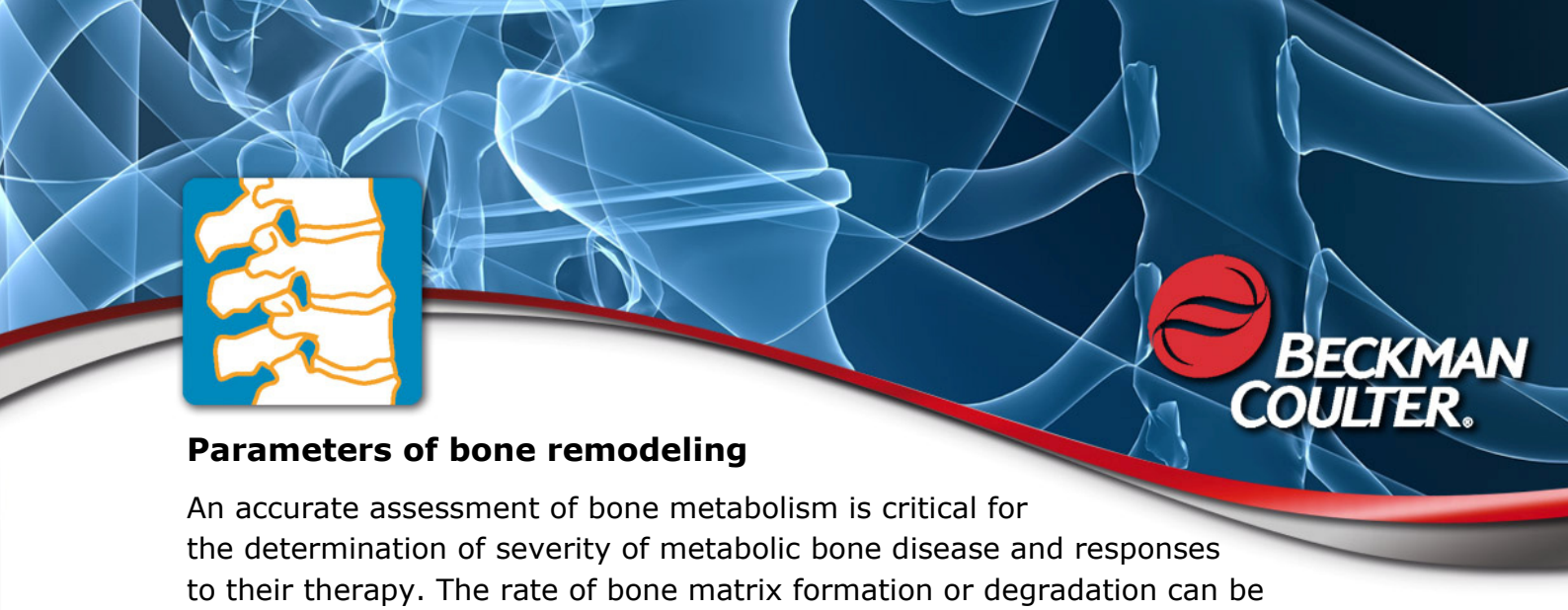
Factor	Effect on bone +/-	Specification
Age	-	Above age 30 loss of bone mass
Physical activity	+	Increases bone density
Calcium	+	Only children, adolescent and in elderly
Fluorids	+	Stimulation of osteoblasts
Hormones		
PTH	-	Stimulation of osteoclasts, inhibition of collagen synthesis in osteoblasts
Calcitriol	+/-	Essential for mineralization, increases intestinal reabsorption of calcium, in higher concentration may act osteolyticaly
Calcitonin	+	Suppression of osteoclasts
Estrogens	+	Increase intestinal absorption of calcium, indirect inhibition of osteoclasts
Testosterone	+	Indirectly by stimulation of muscle growth and as source of estrogens
GH/IGF-1	+	Stimulation of bone formation
Thyroid hormones	+/-	Stimulation of bone resorption which stimulate bone formation
Glucocorticoids (cortisol)	-	Direct inhibition of osteoblast proteins, indirect inhibition of calcium absorption in gut

Bone change throughout life

In healthy children, bone formation is favoured over bone resorption. That implicates normal bone development and skeletal growth. In healthy young adults, bone formation and bone resorption processes are balanced, resulting in no net increase or decrease in skeletal mass. With advancing age, men and women experience an imbalance in bone remodeling in which resorption is slightly greater than formation, resulting in a continuous net loss of bone mass with time. If this imbalance persists, bone mass may decline until the skeleton is insufficient to resist normal mechanical stresses, and it becomes abnormally susceptible to fractures. The excessive loss of bone mass with an increased susceptibility to fractures is a disorder known as osteoporosis, Fig.6.

Fig.6: Progressive spinal deformity in osteoporosis[15]





Parameters of bone remodeling

An accurate assessment of bone metabolism is critical for the determination of severity of metabolic bone disease and responses to their therapy. The rate of bone matrix formation or degradation can be assessed by measuring markers of bone turnover. These markers are classifies into two categories[3]: bone formation markers, Tab.3 and bone resorption markers, Tab.4:

Tab.3: Bone formation markers	
Identification	**Mechanism**
Bone alkaline phosphatase (BAP)	**Secreted by osteoblasts**
Procollagen type I C propeptide	Collagen-based
Procollagen type I N propeptide	Collagen-based
Osteocalcin (bone gla-protein, marked diurnal variation with nadir in morning)	Secreted by osteoblasts
Alkaline phosphatase (not very specific)	Secreted by osteoblasts

Tab.4: Bone resorption markers	
Identification	**Mechanism**
Hydroxyproline (not very specific)	Collagen-based
Pyridinoline	Collagen-based
Deoxypyridinoline	Collagen-based
Tartrate-resistant acid phosphatase	Secreted by osteoblasts
Carboxyterminal cross-linking telopeptide of bone collagen	Collagen-based
Aminoterminal cross-linking telopeptide of bone collagen	Collagen-based

Diseases of bone

Maintaining a strong and healthy skeleton is a complicated process that requires having the right amount of bone with the right structure and composition in the right place. There are many factors that can have negative impact of bone development, Tab.5.

Tab.5: Factors with negative impact on bone

Factor	Cause	Impact on bone	Disease
Genetic disorder	genetic abnormalities	1. week, thin bones 2. bones are too dense	Osteogenesis imperfect Osteopetrosis
Nutrition deficiency	vitamin D, calcium, phosphorus deficiency	weak poorly mineralized bones	Rickets, osteomalacia
Hormonal disorders	1. overactive parathyroid gland (primary hyperparathyroidism) 2. deficiency GH/IGF-1 3. loss of gonadal function, hypogonadism in children 4. cortisol overproduction (Cushing´s syndrome)	1. excessive bone-breakdown, fragile bones 2. decreased bone mass 3.rapid bone loss 4. bone loss	1. high risks of fractures 2. short stature 3. severe osteoporosis 4. high risks of fractures
Medication	Glucocorticoids	thinning of bones	high risks of fractures

Many bone disorders are local, affecting only a small region of the skeleton. Inflammation can lead to bone loss, probably through the production of local resorbing factors by the inflammatory white cells. This process can occur around the affected joints in patients with arthritis. Bacterial infections, such as severe gum inflammation or periodontal disease, can produce loss of the bones around the teeth, and osteomyelitis can produce a loss of bone at the site of infection.

The most common bone diseases and disorders

Osteoporosis

Osteoporosis is the disease of bone that leads to an increased risk of fracture. In osteoporosis the bone mineral density (BMD) is reduced, bone microarchitecture is disrupted and the amount and variety of proteins in bone is altered.

Primary osteoporosis is mainly a disease of the elderly, the result of the cumulative impact of bone loss and deterioration of bone structure that occurs as people age[16]. This form of osteoporosis is sometimes referred to as age-related osteoporosis. Since postmenopausal women are at greater risk, the term "postmenopausal" osteoporosis is also used. Younger individuals (including children and young adults) rarely get primary osteoporosis, although it can occur occasionally. This rare form of the disease is sometimes referred to as **"idiopathic" osteoporosis**, since the exact causes of the disease are not known in many cases.

There are several different forms of idiopathic osteoporosis that can affect both children and adolescents, although these conditions are quite rare[17]. Juvenile osteoporosis affects previously healthy children between the ages of 8 and 14. Over a period of several years, bone growth is impaired. The condition may be relatively mild, causing only one or two collapsed bones in the spine (vertebrae), or it may be severe, affecting virtually the entire spine. The disease almost always goes spontaneously into remission around the time of puberty with a resumption of normal bone growth at that time.

Age-related primary osteoporosis is the most common form of the disease. While it occurs in both sexes, the disease is two to three times more common in women. This is partly due to the fact that women have two

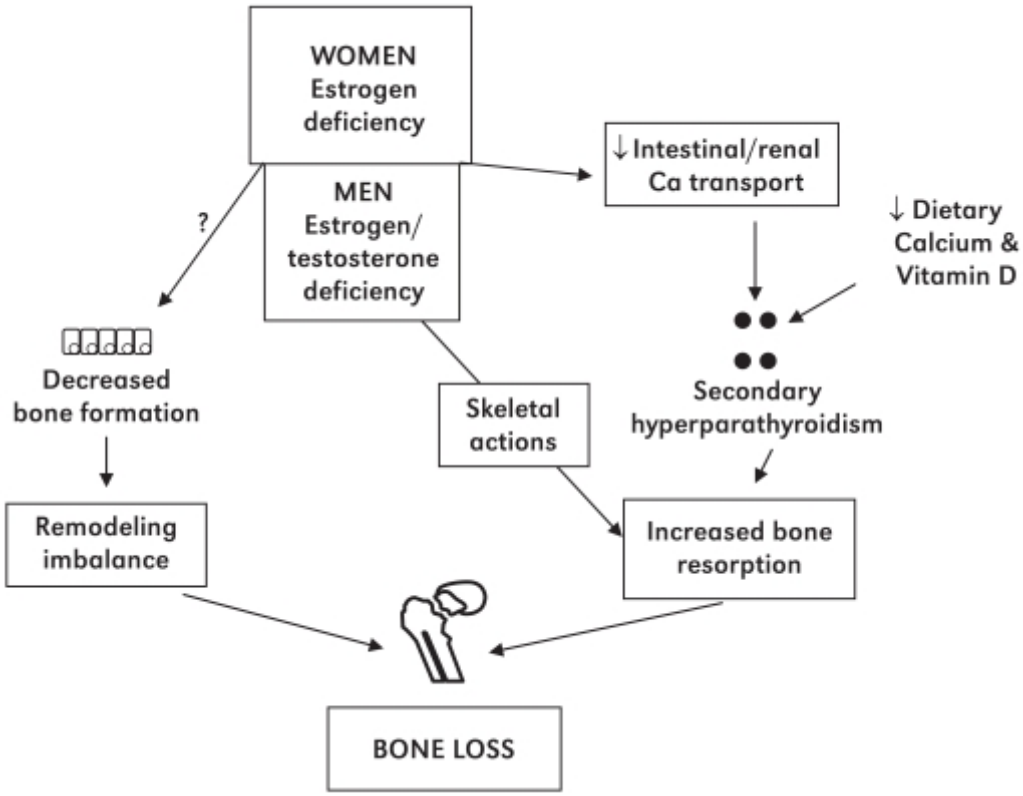
phases of age-related bone loss - a rapid phase that begins at menopause and lasts 4–8 years, followed by a slower continuous phase that lasts throughout the rest of life[18]. By contrast, men go only through the slow, continuous phase. As a result, women typically lose more bone than men do. The rapid phase of bone loss alone results in losses of 5–10% of cortical bone (which makes up the hard outer shell of the skeleton) and 20–30% of trabecular bone (which fills the ends of the limb bones and the vertebral bodies in the spine, the sites of most osteoporotic fractures). The slow phase of bone loss results in losses of 20–25% of cortical and trabecular bone in both men and women, but over a longer period of time[18].

For women, the rapid phase of bone loss is initiated by a dramatic decline in estrogens production by the ovaries at menopause or after ovariectomy. The loss of estrogen action on estrogen receptors in bone, results in significant increases in bone resorption, combined with reduced bone formation. The result is thinning of the cortical outer shell of bone and damage to the trabecular bone structure.

By contrast, the slower phase of bone loss is thought to be caused by a combination of factors including age-related impairment of bone formation, decreased calcium and vitamin D intake, decreased physical activity, and the loss of estrogen's positive effects on calcium balance in the intestine and kidney as well as its effects on bone[18]. This leads to further impairment of absorption of calcium by the intestine and reduced ability of the kidney to conserve calcium. If the amount of calcium absorbed from the diet is insufficient to make up for the obligatory calcium losses in the stool and urine, serum calcium begins to fall. PTH levels will then increase, removing calcium from bone to make up for the loss, Fig.7.

For aging men, sex steroid deficiency also appears to be a major factor in age-related osteoporosis. Although testosterone is the major sex steroid in men, some of it is converted by the aromatase enzyme into estrogen. However, the deficiency is mainly due to an increase in sex hormone binding globulin (SHBG), when both testosterone and estrogens are not available for use by the body.

Fig.7: Bone loss in postmenopausal women and aging men[19]



Secondary osteoporosis: is caused by a wide variety of outside" causes, e.g. alcoholism, smoking, and some diseases along with certain medications (glucocorticoids) and toxic agents that can cause or contribute to the development of osteoporosis.

Ostase (BAP) is a very useful marker in management of patients with osteoporosis.

Paget's disease

Paget‘s disease of the bone (osteitis deformans) is the second most common metabolic illness that typically results in enlarged and deformed bones. It is prevalent in Northern Europe, affecting up to 4% of people over the age of 40 and up to 10% over the age of 60.

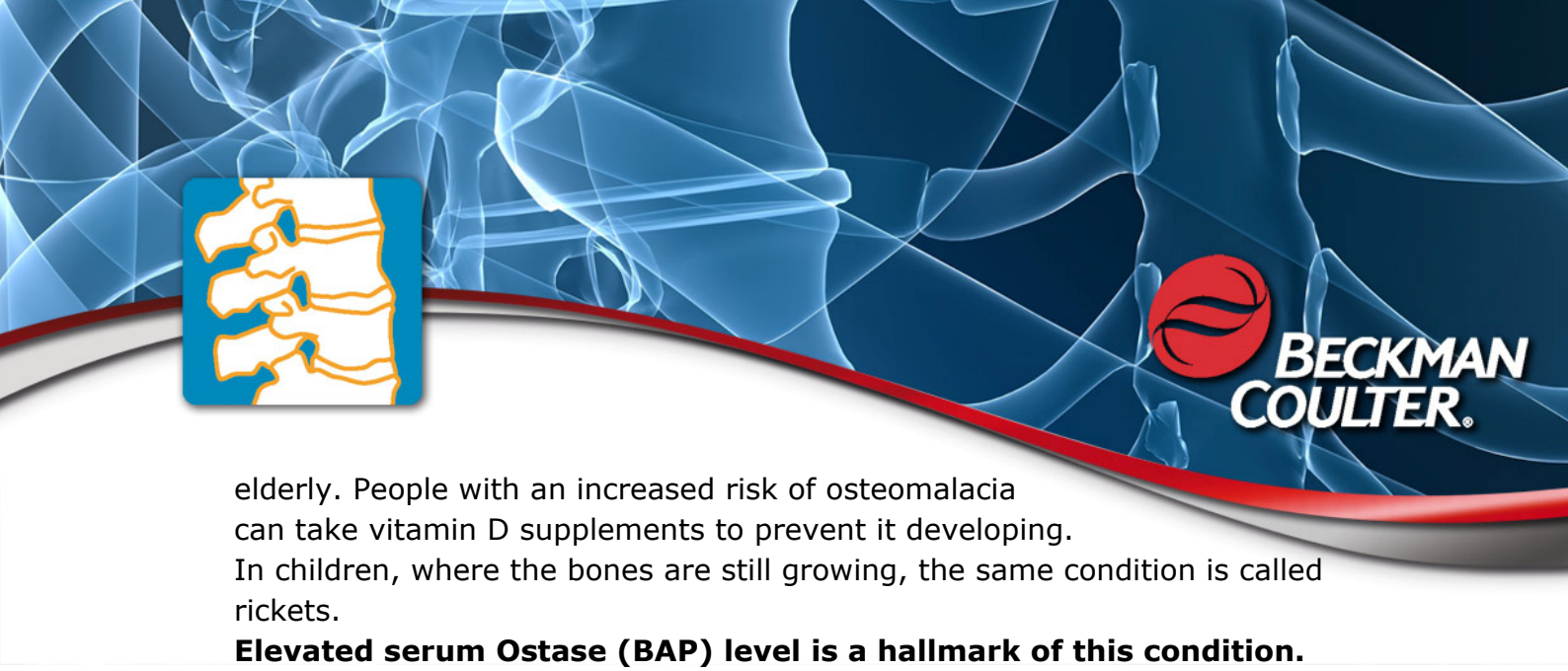
Paget's disease is a disorder of bone remodeling. The precise cause of Paget’s disease is not known, but it appears to be the consequence of both genetic factors and environmental factors, possibly a viral infection. In the initial stages of the disease, osteoclastic activity predominates so that bones become soft and deformed and may fracture. Later increased osteoblastic activity results in thickened deformed, so called “woven” bone. This can trap nerves or leave abnormal bone in the joint areas. Thus, neurological and rheumatological symptoms are associated with Paget's disease. The worst complication is the progression to bone sarcoma, but this occurs rarely (<1%).

This disorder is very often asymptomatic and diagnosed coincidentally from radiological investigation performed for another purpose. The most common complaints in symptomatic patients are pain and deformity.

Paget’s disease can be transmitted (or inherited) across generations in an affected family; 15–40% of patients have a relative with the disorder[20]. Early diagnosis and treatment are very important.
Ostase (BAP) is a very useful marker in management of patients with Paget´s disease.

Osteomalacia and rickets[21]

It is the term used to describe the pathological condition in bone in which the osteoid matrix (the proteinaceous scaffolding in bone) remains uncalcified. Osteomalacia is a condition affecting adults, the bones become weak and softer than normal. Symptoms include bone pain and muscle weakness. The condition is usually caused by vitamin D deficiency, and can be treated by vitamin D supplements. Some people are more at risk of osteomalacia, particularly pregnant or breast-feeding women, black or Asian people and the



elderly. People with an increased risk of osteomalacia can take vitamin D supplements to prevent it developing.
In children, where the bones are still growing, the same condition is called rickets.
Elevated serum Ostase (BAP) level is a hallmark of this condition.

Renal osteodystrophy or chronic kidney disease-mineral and bone disorder[22]

This condition is characterized by a stimulation of bone metabolism caused by an increase in PTH and by a delay in bone mineralization that is caused by decreased kidney production of Calcitiol. In addition, some patients show a failure of bone formation, called adynamic bone disease. Patients with chronic renal disease are in the risk of developing of renal osteodystrophy. At the beginning, renal osteodystrophy may not exhibit any symptoms. If it does show symptoms, they include bone pain, joint pain, bone deformation or bone fracture. By the time the patient progresses to end-stage renal failure, clinical manifestations of the disease appear, including bone cysts that result from stimulation of osteoclasts by the excess PTH.
Determination of Ostase and PTH are useful markers in this disease.

Primary hyperparathyroidism[21]

Primary hyperparathyroidism causes hypercalcemia (elevated blood calcium levels) through the excessive secretion of PTH, usually by an adenoma (benign tumors) of the parathyroid glands. The other possible causes can be hypophosphatemia, hypercalciuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis and sometimes neuropsychiatric and neuromuscular problems.
Blood tests are in this case performed to look for increased levels of PTH, calcium, and BAP and lower levels of phosphorus.
About 90% of the patients with primary hyperparathyroidism have elevated PTH levels. The remaining patients have normal PTH levels (inappropriate for the elevated calcium level). About 40% of the patients with primary

hyperparathyroidism have blood phosphorus levels <2.5 mg/dL and about 80% have blood phosphorus <3.0 mg/dL.

Hyperparathyroidism can also **be secondary** in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. PTH is increased before total of free calcium becomes abnormally low, a consequence of homeostatic mechanism for maintenance of blood calcium. Consequently, PTH is more sensitive than calcium for identifying secondary hyperparathyroidism.
Determination of PTH is useful marker in this disease.

Hypoparathyroidism

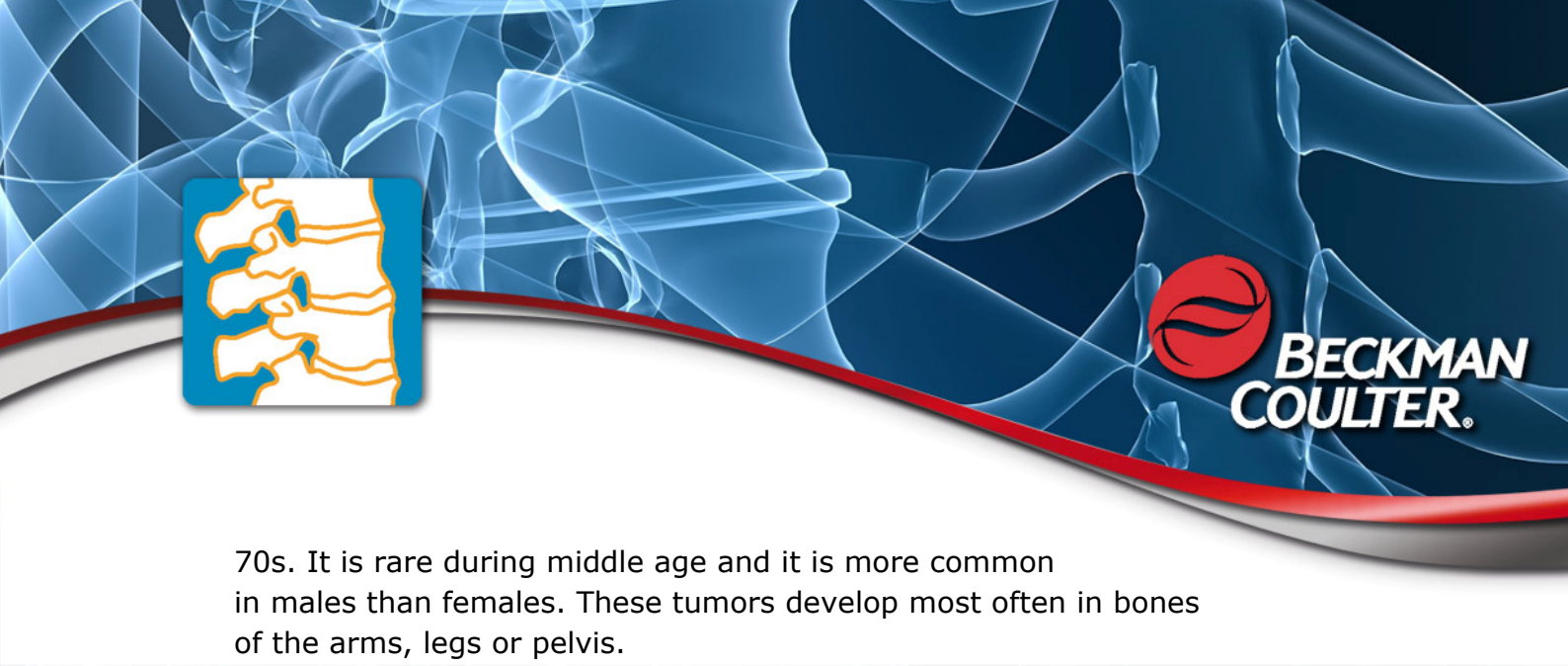
Hypoparathyroidism is most commonly secondary due to thyroid surgery, but can also occur on an autoimmune basis. The symptoms of hypopara-thyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.
Low blood calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH.
Determination of PTH is useful marker in this disease.

Diagnosis of malignancy-associated hypercalcemia

A low PTH level and high phosphorus level in a hypercalcemic patient suggest that the hypercalcemia is not caused by PTH or PTH-like substances.
A low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid hormone related peptide (PTHrP). PTHrP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types.
Determination of PTH and PTHrP are useful markers in this disease.

Bone cancer (osteogenic sarcoma or osteosarcoma[23])

It is one of the most common primary bone cancers. This cancer starts in the bone cells. It most often occurs in young people between the age of 10 and 30, but about 10% of osteosarcoma cases develop in people in their 60s and



70s. It is rare during middle age and it is more common in males than females. These tumors develop most often in bones of the arms, legs or pelvis.
Very high BAP levels are present in patients with osteogenic bone cancer.

Prostate cancer

Prostate cancer metastasizes primarily to the skeleton and only occasionally to the lungs and the liver. **The total PSA and BAP assessments in the patients with the risk of developing bone metastases are used to monitor the disease and may avoid unnecessary bone scintigraphies.**

Hypophosphatasia[24]

Hypophosphatasia is a rare inherited disorder[25] characterized by defective bone and teeth mineralization, and deficiency of serum and BAP activity. The prevalence of severe forms of the disease has been estimated at 1/100 000. The symptoms are highly variable in their clinical expression, which ranges from stillbirth without mineralized bone to early loss of teeth without bone symptoms. Clinical symptoms are respiratory complications, premature craniosynostosis, widespread demineralization and rachitic changes in the metaphyses. The childhood form is characterized by skeletal deformities, short stature, and waddling gait. The adult form is characterized by stress fractures, thigh pain, chondrocalcinosis and marked osteoarthropathy. The disease is due to mutations in the liver/bone/kidney ALP gene encoding the tissue-nonspecific ALP.
The BAP levels are decreased in this disease.

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