Oral Biology
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Lecture - 10
Mineralization dynamics - Part 1

Today here we are to learn about Mineralization dynamics and I am here Doctor Ramya to present you about the Mineralization dynamics.

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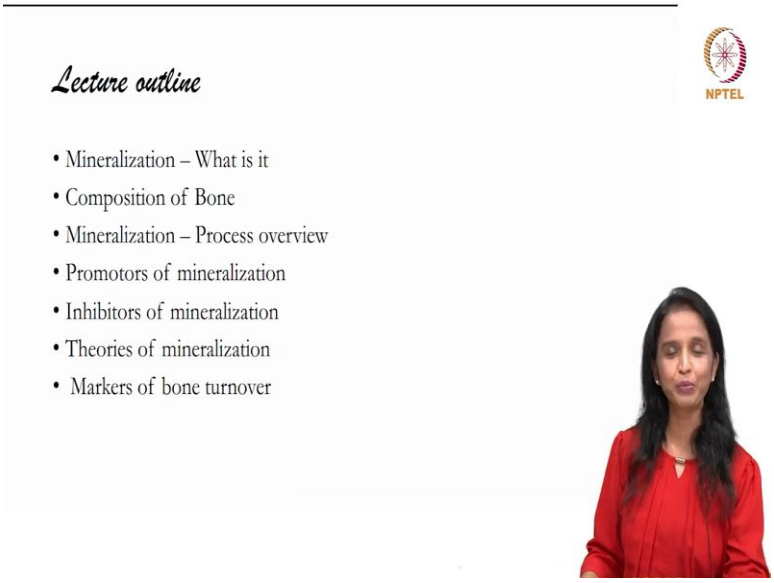

So, this lecture outline would be covering upon all the aspects of mineralization which consists of what is mineralization all about, the composition of bone, the mineralization process overview, promoters of mineralization, inhibitors of mineralization and then we move on to theories and markers of bone turnover.

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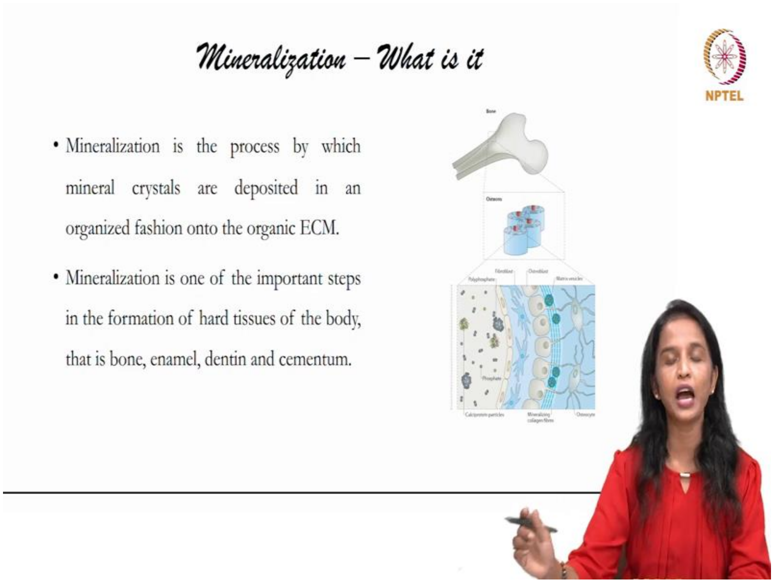

So, first we have to learn about what mineralization is all about. What is it about? And mineralization is the process by which mineral crystals are deposited in an organized fashion in the organic extracellular matrix. So, that is the most important statement and it is one of the most important steps in the formation of hard tissues of the body; the hard tissues of the body being the bone, the cementum, the enamel and the dentin.

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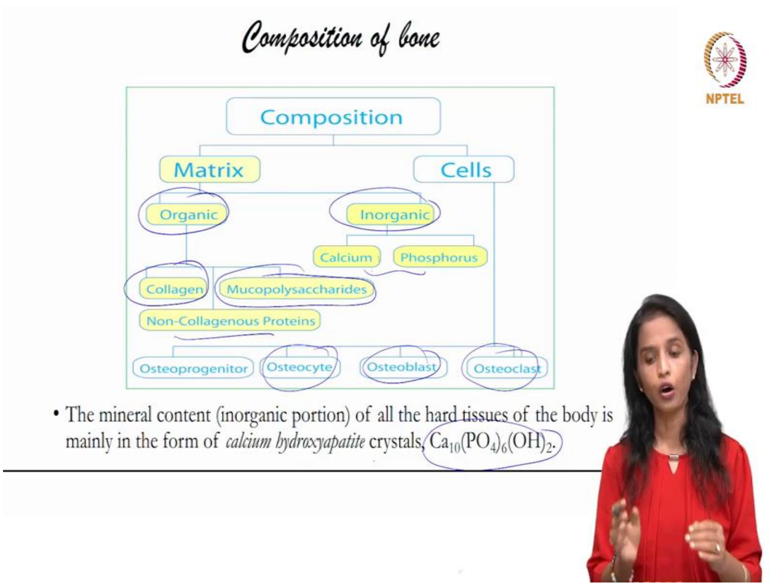

So, here before we step on to knowing about the mineralization we have to learn about the composition of bone which is the most representative hard tissue in the body or the more widely present hard tissue in the body. So, knowing about the composition would just give an overview of what the hard tissues are all about. So, any hard tissue would have a basic structure that is the matrix and then the mineral component.

we have overview that is your organic and then your inorganic component. So, the organic matrix is the one which would be laid first and following which the mineralization steps happen in a sequence of events.

So, this organic component has the collagen which is the most important part of the bone and this collagen in the bone mostly is type 1. So, type 1 is actually the predominant collagen in the hard tissues and further we have mucopolysaccharides and other non collagenous proteins which are mentioned as NCP’s.

There are cellular elements in the matrix as well. So, the cellular elements mean bone formative cells that is your osteoblast and then we have the bone resorptive cell that is your osteoclast and then the resting osteoblast is called as the osteocyte and then for all these to form there are progenitor cells. And then we move on to the inorganic composition; the inorganic composition again are made up of many ions the predominant ions of the bone are your calcium and phosphorus.

So, they form the most important vital component and this inorganic portion is actually in the form of calcium hydroxyapatite and this calcium hydroxyapatite is actually the principal crystal which is present in the hard tissues of the body name it the bone, the enamel, the dentin and the cementum.

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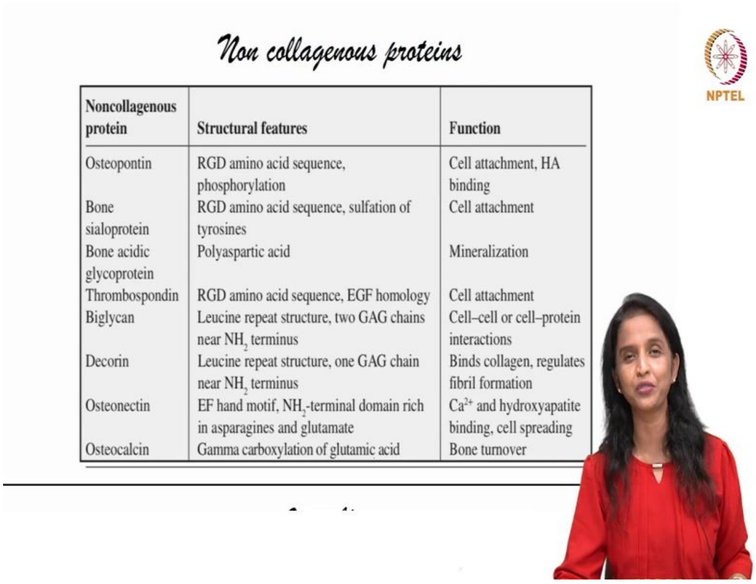

Noncollagenous protein	Structural features	Function
Osteopontin	RGD amino acid sequence, phosphorylation	Cell attachment, HA binding
Bone sialoprotein	RGD amino acid sequence, sulfation of tyrosines	Cell attachment
Bone acidic glycoprotein	Polyaspartic acid	Mineralization
Thrombospondin	RGD amino acid sequence, EGF homology	Cell attachment
Biglycan	Leucine repeat structure, two GAG chains near NH_2 terminus	Cell–cell or cell–protein interactions
Decorin	Leucine repeat structure, one GAG chain near NH_2 terminus	Binds collagen, regulates fibril formation
Osteonectin	EF hand motif, NH_2-terminal domain rich in asparagines and glutamate	Ca^{2+} and hydroxyapatite binding, cell spreading
Osteocalcin	Gamma carboxylation of glutamic acid	Bone turnover

And then further we have the non collagenous proteins. So, the non collagenous protein as already mentioned are also shortly mentioned as NCP’s and these are very important and they play a very vital role in the bone metabolism, regulation and the remodeling status of the bone.

So, to quickly go through the non collagenous proteins we have the osteopontin, the bone sialoprotein, glycoprotein, thrombospondin, biglycan, decorin, osteonectin and osteocalcin and these have a wide variety of function ranging from cell attachment mineralization cell attachment and fibril formation, calcium binding, cell spreading and bone turnover.

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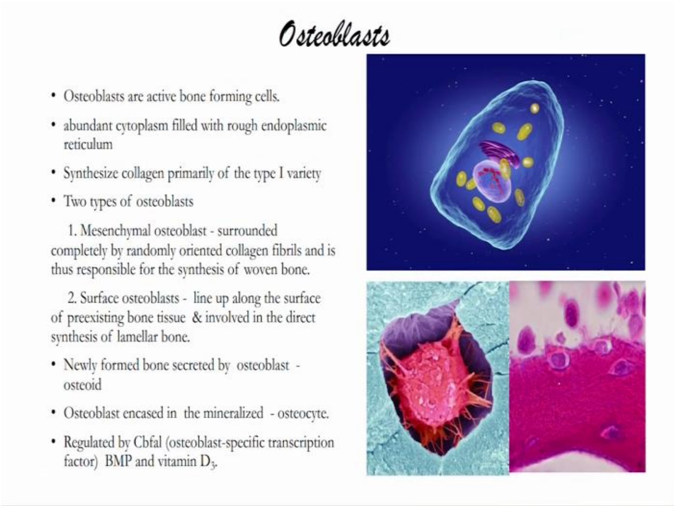

So, the first thing here the most important one the most important formative cell that is the osteoblast. The most important cell in the bone or any hard tissue or specifically the hard tissue which is bone and dentin and cementum have some formative cell called as osteoblast whereas, it is different in case of enamel where it is called as ameloblast. So, this osteoblast actually has a very prominent polygonal outline and this polygonal outline is actually actively bone forming cells and it is actually very prominent and plump in appearance.

It is polygonal and it has an abundant cytoplasm and numerous cellular organelles present good enough to be secretory in nature or to secrete the bone component. The main predominantly secretory material which the bone actually secretes is the type 1 collagen and that is what is the most important organic component of the hard tissues and then we see that osteoblast as the name implies which is the formative cell of the bone.

There are two types of osteoblasts the mesenchymal and the surface. As the word indicates mesenchymal osteoblasts are those which are actually surrounded by the collagen fibers or it is intermingled between the collagen fibers and are responsible for formation of woven bone. Whereas, your surface osteoblasts are the one which have present on the surface of the bone and are involved in direct synthesis of lamellar bone.

So, the moment being you are hearing the word woven bone and lamellar bone; woven bone is a newly formed bone whereas, your lamellar bone is actually the matured bone which is sheet like in appearance. And then we have another important term which is actually should be remembered as the osteoblast secretes the bone it actually secretes bone around this area and then gets entrapped in its own matrix and after it gets entrapped in its own matrix it loses many of its secretory cellular organelles and that goes into a resting phase called as osteocyte.

During that process there are some it actually develops lot of processes so that it can actually derive nutrition from the external source. So, this picture is actually an osteocyte and this is what is actually seen in the histopathological image. So, the one which is outside is called as a surface osteoblast and here it is started secreting the bone matrix and it gets entrapped in its own matrix and you can see an osteoblast getting into a resting phase that is your osteocyte.

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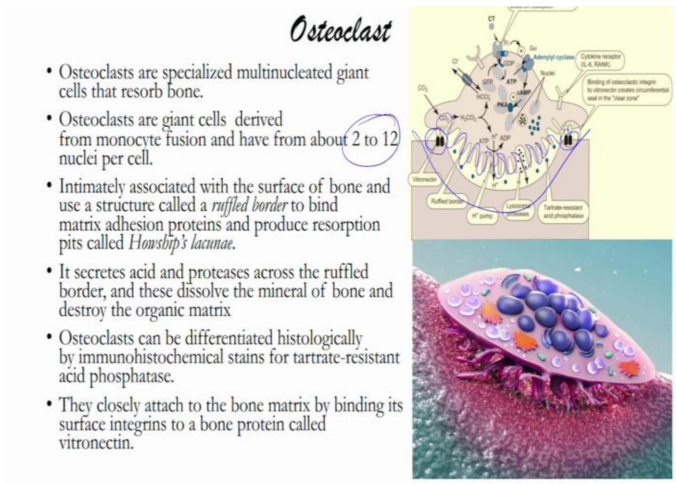

And then further we move on to osteoclast which is actually very important. The osteoclast as the name indicates it is actually involves in the resorption of the bone. And this osteoclast is also called as giant cells because of the size and also because of many number of nucleus present in the cytoplasm.

So, the number of nucleus is very high and there are almost more than 2 to 12 nuclei per cell and the structure of the osteoclast has a periphery which is ruffled in appearance which is thrown into folds and that actually increases the surface area of the osteoclast to get attached to the bone and at the same time derive lot of activity or conduct lot of activity because of that ruffle the system present there.

And this osteoclast is actually present on the bone surface in an area called as Howship's lacunae. And then we can see that this particular osteoclast is getting attached to the bone at a point through a molecule called as vitronectin and this vitronectin is very important so that it actually helps to seal establish a tight seal on the surface of the bone so that the acid proteases that are secreted from the osteoclast do not escape onto the adjacent area.

It is very clearly more precisely focused in the area where the resorption has to take place. So, that is how it happens and then further we can see that these osteoclasts can be very easily histologically identified and also specifically identified by advanced methods that is immunohistochemistry through tartrate resistant acid phosphatase enzyme straining.

So, this acid phosphatase is actually a very important enzyme which is secreted by the osteoclast and it is an important diagnostic marker. So, to be more specific the tartrate resistant type of acid phosphatase enzyme is actually the one which is very importantly regulating the osteoclast itself and it helps to for the osteoclast to conduct its resorptive activity.

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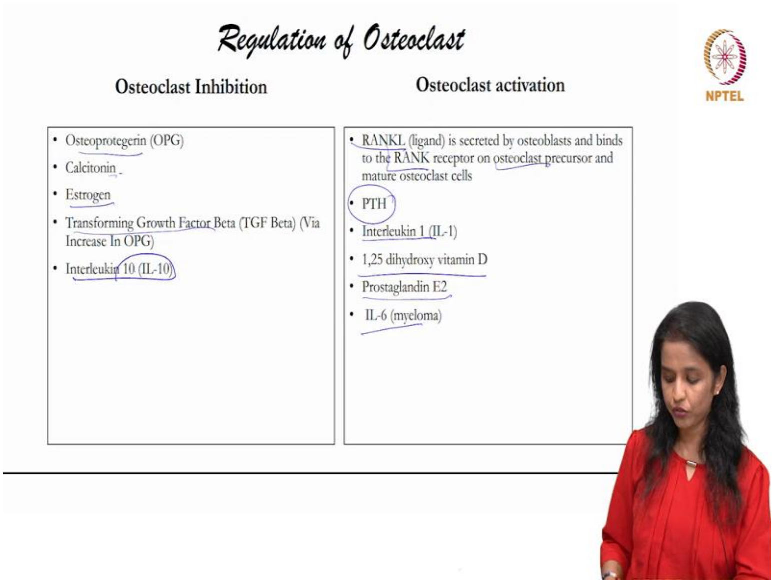

And this important thing is that the osteoclast has an array of inhibitors and activators as well. So, the regulation of osteoclasts is so closely governed by array of activators; the activators include the RANKL ligand which binds on to the RANK receptor on the osteoclast and then we have the most important hormone here the parathyroid hormone, Interleukin 1 and we have your vitamin D here, prostaglandins and Interleukin 6 to be more precise and then further we have osteoclast inhibition happening from because of osteoprotegerin, calcitonin, estrogen, TGF beta and Interleukin 10.

So, all these are very important regulators which either activate or which inhibit. So, there are a series of molecules or an array of molecular molecules which are responsible to regulate the osteoclastic activity.

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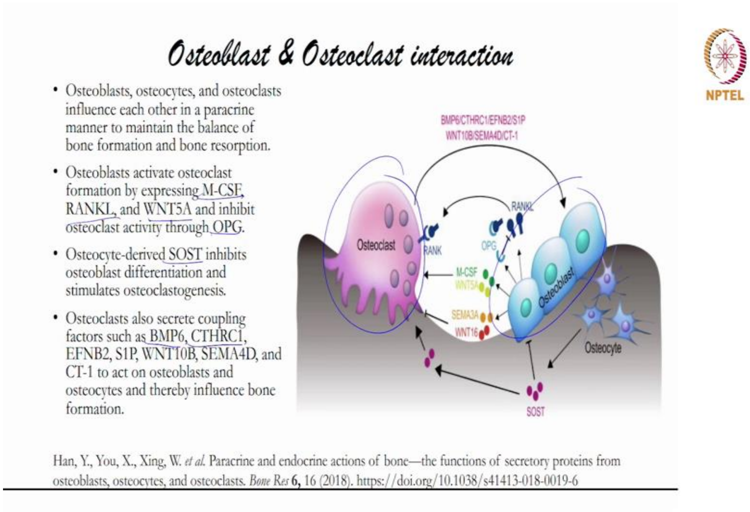

And then further we have an important understanding to know here is that the osteoblast and the osteoclast do interact with each other. So, how do they interact? They act through a system called as paracrine signaling. So, this paracrine signaling is when there is a release of the signaling agents or the molecular signals to the neighboring cells that is a paracrine activity.

So, here we can see that the osteoblast trigger paracrine activity through your colony stimulating factor, RANKL, WNT pathway and also inhibit osteoclastic activity through your osteoprotegerin. So, that is what you can see they are closely associated with so many molecules and then there is an interplay of molecules here. Osteocyte which is actually resting also has lot of molecules which actually take care of that particular resting cell.

So, why is that important see as the bone is formed and it is in the resting phase still at any time the particular resting osteocyte has to come into play and then take care of the bone remodeling process. So, for that to happen there are again a lot of genetic events or genetic factors involved and then we also have SOST which inhibits osteoblast differentiation and stimulates osteoclastogenesis.

So, it is all a very tightly regulated interplay of network of molecular events which controls the osteoblast and the osteoclast interaction. And then further osteoclast is actually controlled by your BMP and then we have your CTHRC1 and EFBNT, S 1 IP and then we have WNT and CT which is acting on the osteoblast and the osteocytes and all are very very important for influencing the bone formation.

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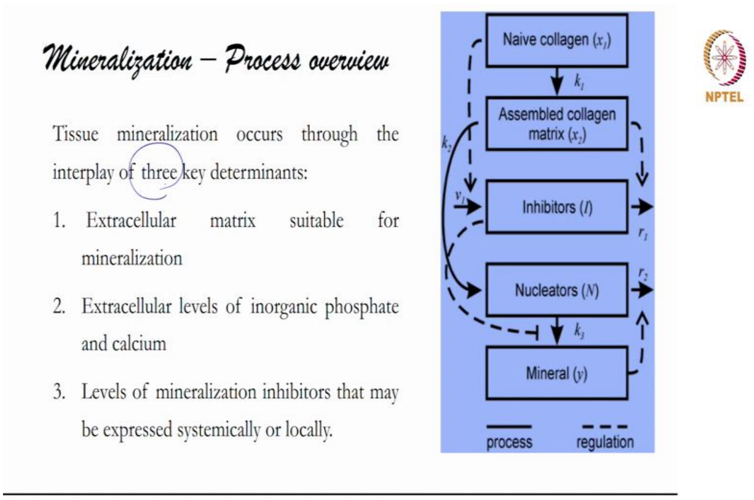

So, as an overview of bone formation we can see that the tissue mineralization occurs through most important three key determinants. So, this is the most important point over here three key determinants are important for mineralization. So, what are those key determinants? So, the first one is your matrix. So, that is the ground substance, the foundation, the template over which you have your inorganic phosphates and calcium getting deposited.

And then how much of it has to get deposited is controlled by the mineralization inhibitors those can be locally acting or they can be systemically acting. So, those that is about the process overview. So, to repeat the process overview we have three important determinants the matrix, the ions and then the inhibitors.

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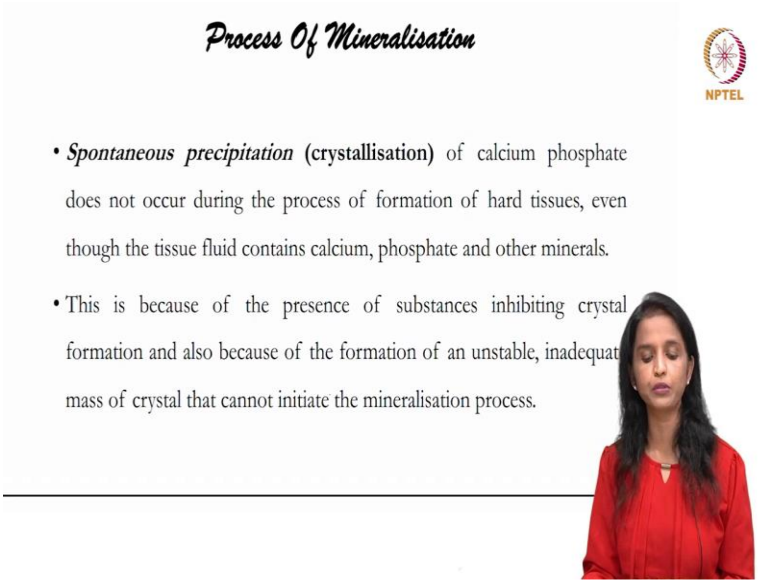

So, the process of mineralization happens by the most important spontaneous precipitation; precipitation or crystallization of calcium phosphate and occurs in the formation of your hard tissues. And even it occurs even if the particular surrounding extra cellular fluid does not contain enough ions it happens through a very tightly regulated system.

So, this is because of there are some substances which are actually inhibiting the crystal formation and then there are some substances which are actually promoting the crystal formation. So, spontaneous precipitation actually does not occur during the process of formation of hard tissues even though the tissue fluids are containing calcium and phosphate and other minerals.

So, it is all tightly regulated.

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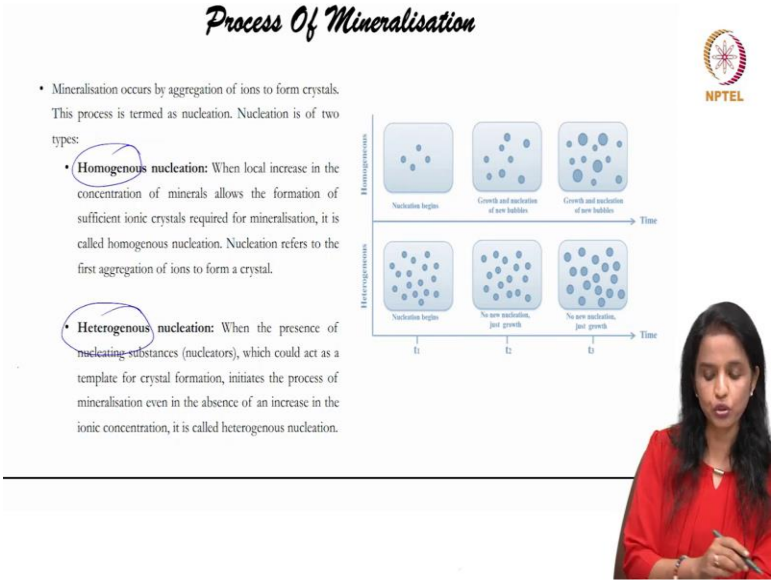

The process is in overview is actually of two types that is your homogeneous nucleation and heterogeneous nucleation. So, homogeneous nucleation is very simple to understand as the name suggests it is the increase in the concentration of mineral allowing the formation of sufficient ionic crystals required for mineralization. So, nucleation refers to the first aggregation of ions to form a crystal.

So, this actually happens because of local increase in concentration of minerals. Then we have the heterogeneous mineralization where the presence of nucleating substances are important and that acts as a template for crystal formation. So, what happens is even in the absence of an increased ionic concentration there is crystallization and this is called as heterogeneous nucleation this can happen only when the nucleators are there.

So, again there are two types of crystallization the homogeneous and the heterogeneous. Homogeneous is actually a very low due to local increase in the ionic content the homogeneous crystallization takes place whereas, the heterogeneous nucleation takes place because of the presence of a nucleator agent and then there is deposition of ions even in the absence of a adequate concentration. So, that is your heterogeneous nucleation.

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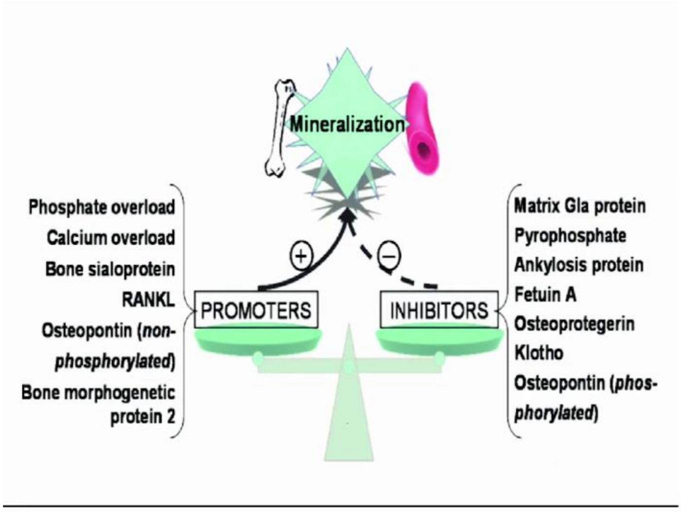

This again is a very nice overview of what mineralization is all about there are promoters and inhibitors. So, which are the promoters and which are the inhibitors? So, phosphate overload definitely is a promoter and then we have calcium overload and then bone sialoprotein which is shortly called as BSP's and then we have the RANKL, osteopontin and bone morphogenic protein.

So, we have six promoters and then inhibitors we have Matrix Gla Protein as called as MGP, pyrophosphate, ankylosis protein, fetuin, osteoprotegen, klotho, osteopontin.

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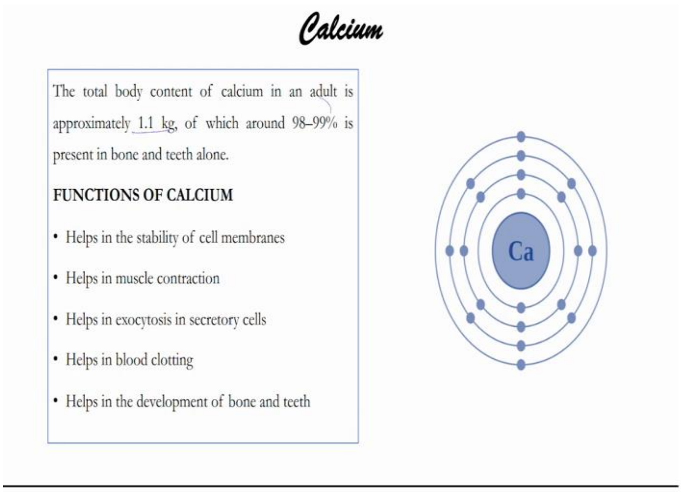

Then in one by one the most important promoter agents are the first to know is your calcium. So, calcium is given lot of importance here in today’s lecture also because that forms a most important role in mineralization.

So, the total body content of calcium I mean is about 1.1 kg and it accounts to almost 98 to 99 percent which is present in bone and teeth. So, in addition to mineralization it also actually helps in stability of cell membrane, muscle contraction, exocytosis in secretory cells, blood clotting and development of bone and teeth.

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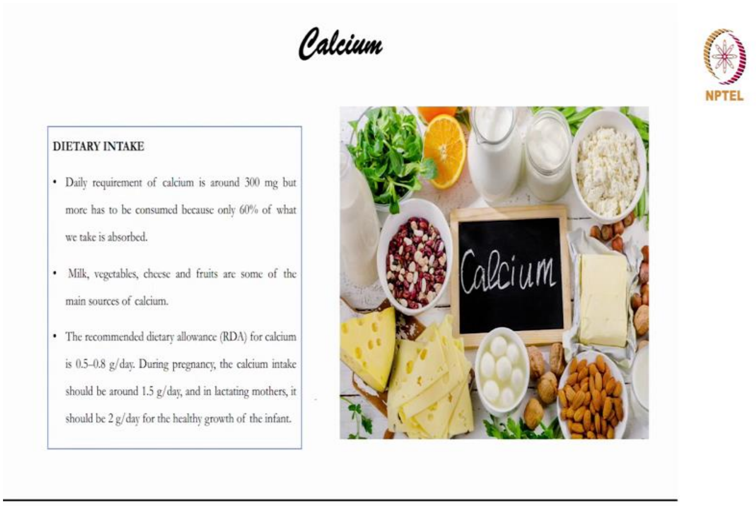

Dietary calcium intake here is again a very important point to remember here in mineralization dynamics because the part of calcium gets complete once you know how much of dietary intake has to be there. So, around at least minimum of 300 milligrams is expected to be consumed and those are available as milk, vegetables, cheese and fruits. And then we have the recommended RDA allowance that is very important to be calculated per kilogram requirement of the human body that is 0.5 to 0.8 grams per day.

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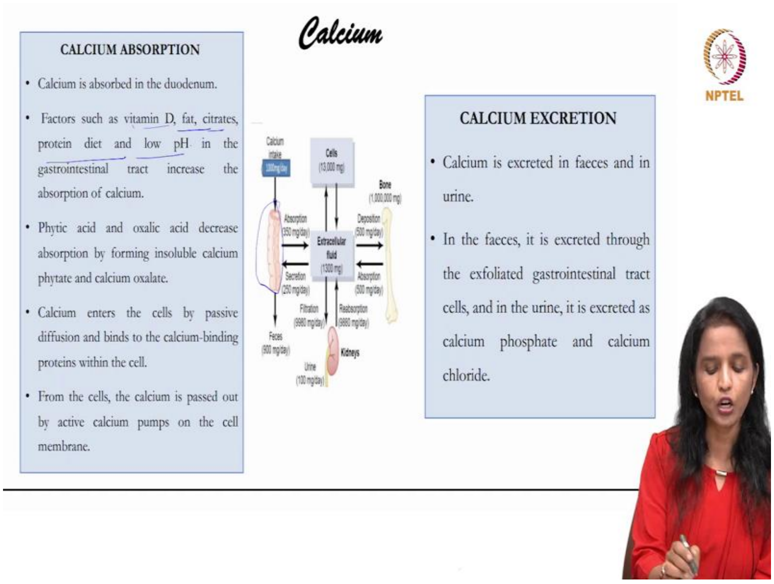

And the requirement actually increases when there is a increased demand. And then calcium absorption and excretion are very important. So, you can see that the calcium is getting absorbed in the duodenum and then there are so many factors which are helping in absorption or favoring absorption that is your vitamin D, fat, citrates, protein diet and low pH in the gastrointestinal tract.

Further the phytic acid and oxalic acid decrease absorption by forming insoluble calcium phytate and calcium oxalate and calcium also enters the cell by passive diffusion and then further you can see that calcium is excreted in the urine and the faeces. So, this is actually excreted through the exfoliated gastrointestinal cells and it is excreted as calcium phosphate and calcium chloride.

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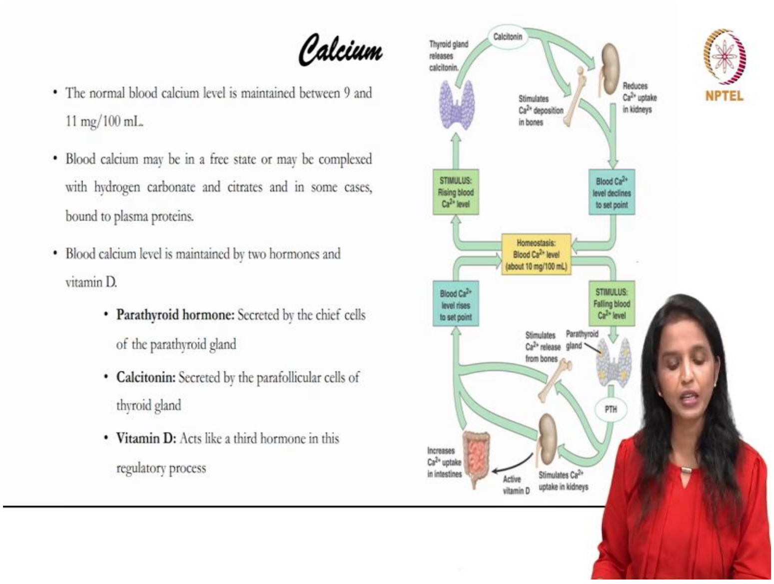

And then we have the calcium ions here the normal calcium ions is about 9 to 10 or 11 milligrams per 100 ml and the blood calcium is usually as in a free state or it might be in a conjugated with hydrogen carbonate and citrates. And the blood calcium level is actually maintained by most important hormones which was already said that is the parathyroid hormone and the calcitonin.

There are other hormones as well which we will be quickly reading through in addition to vitamin D.

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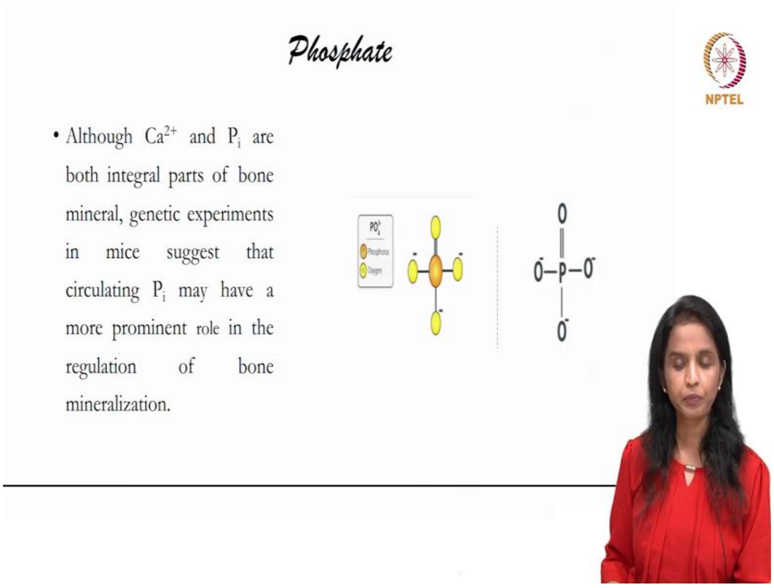

And the most important inorganic ion next to calcium is your phosphate and these are also very important and play a very dominant role in forming the mineralized inorganic component of the hard tissues.

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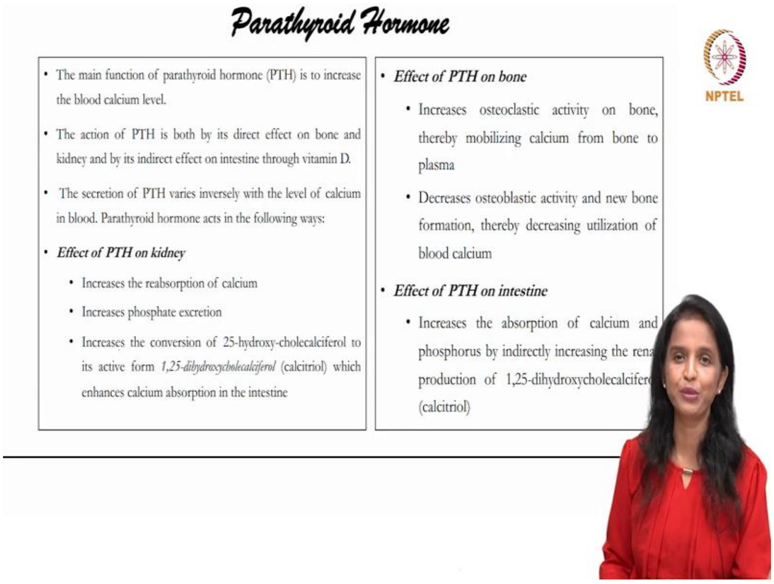

The next important part of this promoters of your mineralization is that now we are going to look into the hormonal part. So, parathyroid hormone is actually secreted by the parathyroid gland and these are very important hormones which are acting through the kidney on the bone and on the intestine to maintain adequate levels of calcium in the blood. So, these actually are very important regulators of your mineralization mechanism.

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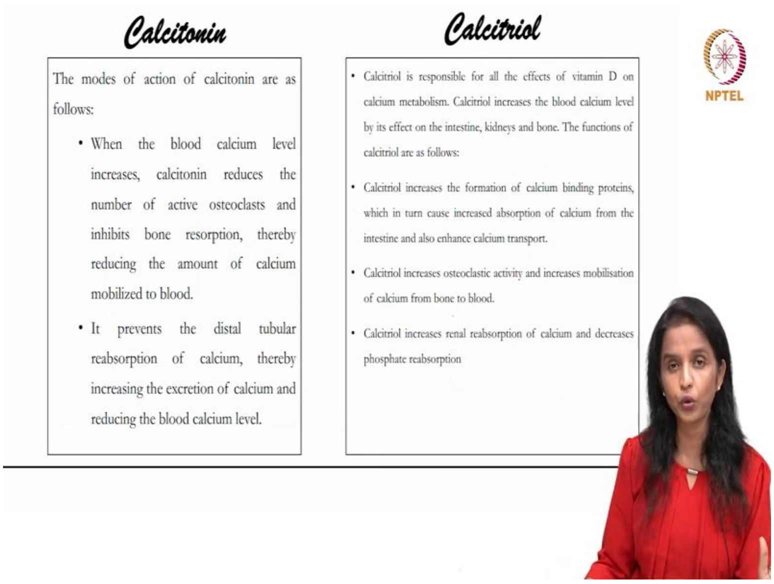

And then the next two important hormones are your calcitonin and calcitriol. So, what happens with calcitonin is that the blood calcium level increases, if it increases calcitonin reduces the number of osteoclast and inhibits bone resorption. So, the main activity of calcitonin is that it actually reduces the bone resorption, whereas calcitriol is responsible for all the effects of vitamin D and calcium metabolism and increases the formation of calcium binding proteins.

So, calcium calcitriol increases osteoclastic activity and increases mobilization of calcium from blood into the bone.

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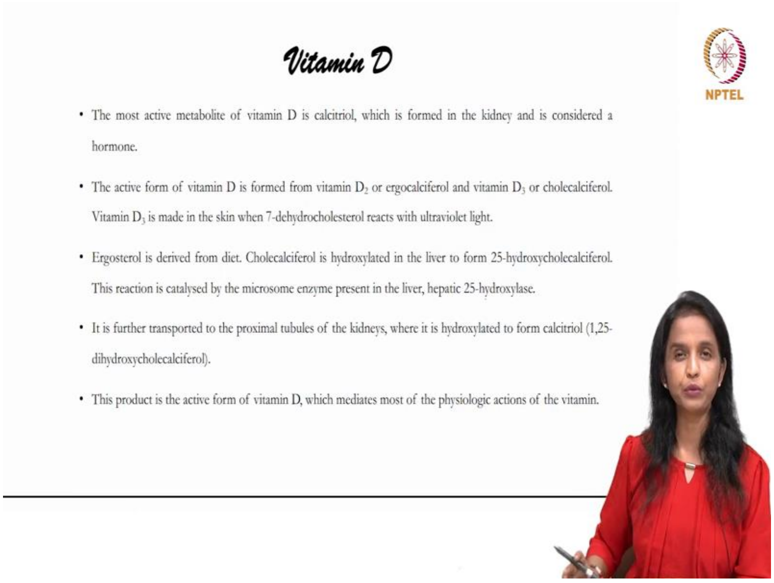

And further we have the vitamin D the most active part of vitamin D is your calcitriol and which is formed in the kidney and it is considered as a hormone. So, this vitamin D again is a very very important vital or vital agent in mineralization and we know that just getting exposed to sun itself would give you an ample amount of vitamin D to your body. So, it is a very very important body to stay very strong because this vitamin D is what actually helps in strengthening your mineralization.

So, the most active metabolite of vitamin D is calcitriol and this calcitriol is actually very important part and mediates the physiological action of the vitamin.

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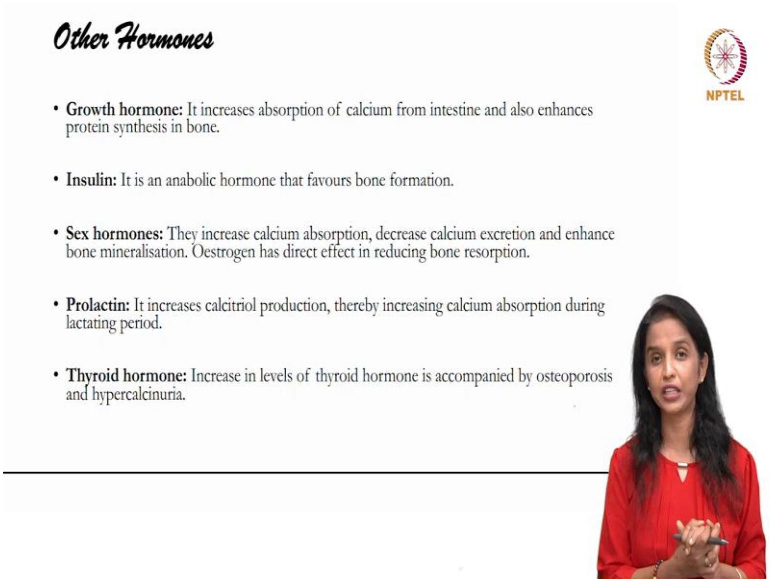

Other hormones in addition to what we saw till now that is your parathyroid hormone and then we saw calcitonin, calcitriol, vitamin D additionally we have the growth hormone, insulin, the sex hormone especially the oestrogen, prolactin and thyroid hormone which are very important and have a significant role on the mineralization of the hard tissues.

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