Biomechanics of Joints and Orthopaedic Implants
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Lecture 40
Bone Ingrowth and Mechanoregulatory Principles

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Good afternoon everybody, welcome to the second lecture of module 8 in the NPTL online certification course of the biomechanics of joints and orthopaedic implants. This lecture is on bone ingrowth and Mechanoregulatory principles.

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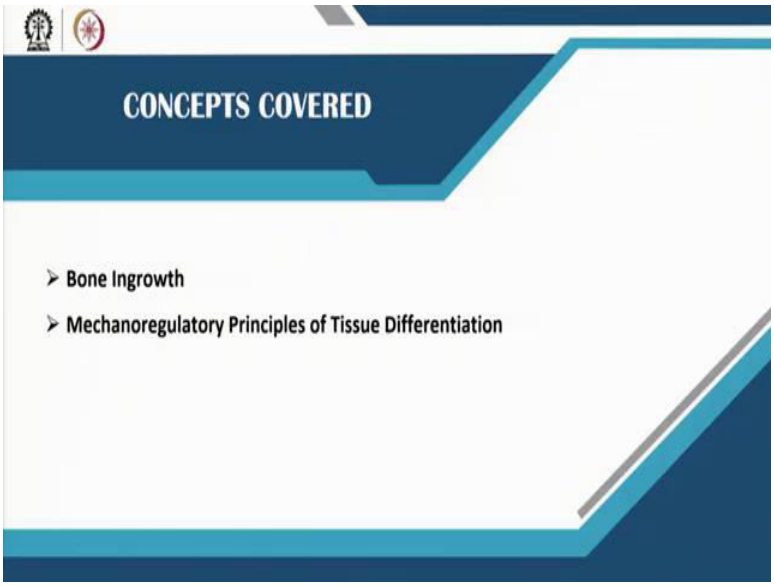

In this lecture, we will discuss bone ingrowth and the different mechanoregulatory principles of tissue differentiation.

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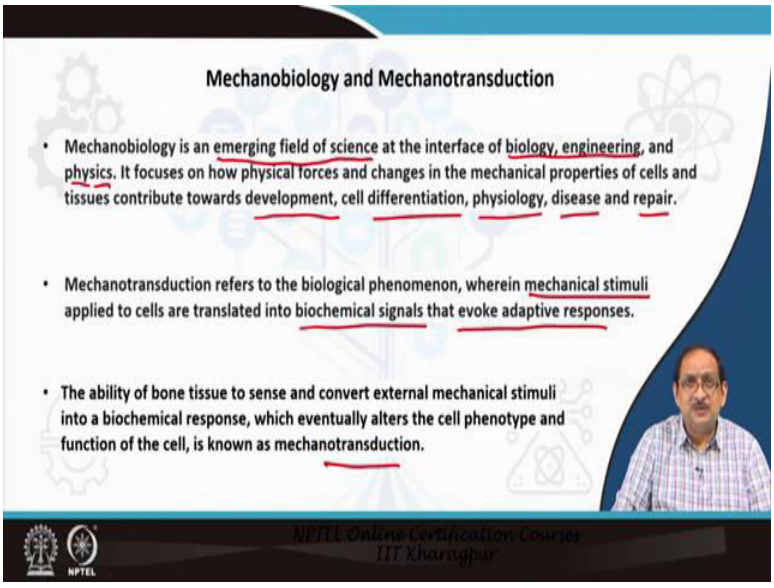

Now, before we move into the details of the lecture's content, we need to understand two important terms used in this area. One is mechanobiology; the other is mechanotransduction. Mechanobiology is an emerging field of science at the interface of biology, engineering and physics.

It focuses on how physical forces and changes in cells and tissues' mechanical properties contribute towards development, cell differentiation, physiology, disease, and repair. Now, mechanotransduction refers to the biological phenomenon wherein the mechanical stimuli applied to cells are translated into biochemical signals. So, the mechanical stimuli applied to the cells are translated into biochemical signals that evoke or generate adaptive responses.

The ability of bone tissue to sense and convert external mechanical stimuli into a biochemical response, which eventually alters the cell phenotype and function of the cell, is known as mechanotransduction. So, mechanobiology is an interdisciplinary field of science, whereas mechanotransduction is a biological phenomenon.

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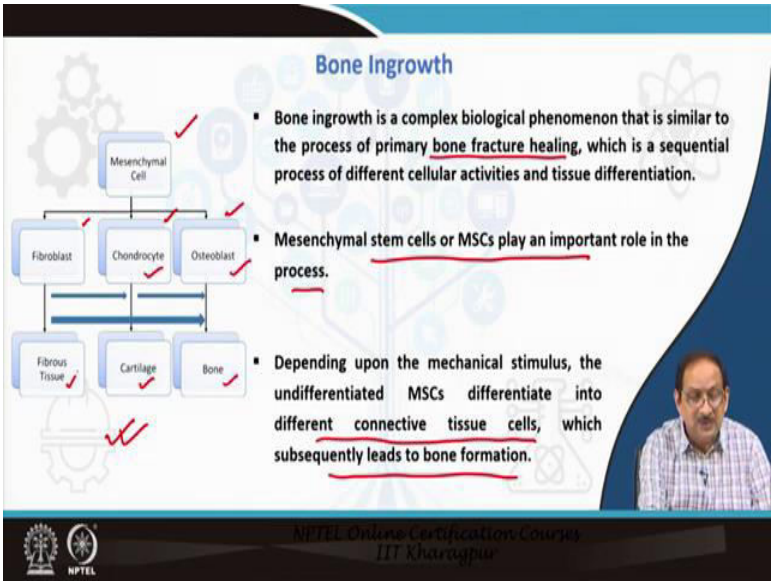

Let us now discuss the process of bone ingrowth. Bone ingrowth is a complex phenomenon similar to primary bone fracture healing, which is a sequential process of different cellular activities and tissue differentiation. The mesenchymal stem cells, or MSCs, play an essential role in the process, as discussed in the earlier lecture 8.1.

Depending on the mechanical stimulus, the undifferentiated MSCs differentiate into different connective tissue cells, leading to bone formation. The influence of mechanical stimulus on tissue differentiation is of particular interest from implant design in the particular uncemented

porous-coated implant. In the absence of any growth factor, mechanical stimuli alone could regulate progressive tissue differentiation.

Now, on the left, the flowchart summarizes the tissue differentiation process. So, from mesenchymal stem cells, the cells can differentiate into fibroblast, chondrocyte, and osteoblasts, and you can see that bone tissue can be formed from osteoblasts, cartilage can be formed from chondrocyte, and fibrous tissue can be formed from fibroblasts.

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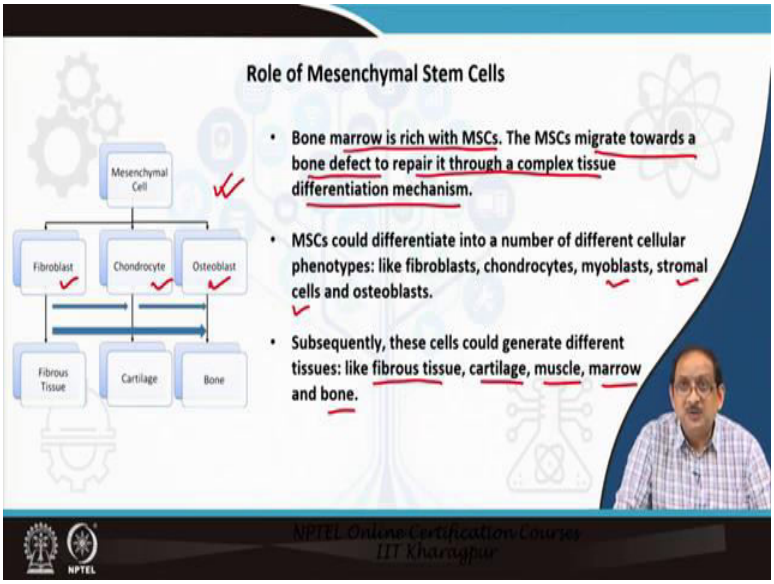

Now, let us move into the role of mesenchymal stem cells. The bone marrow is rich in mesenchymal stem cells. So, the MSCs migrate towards a bone defect in granulation tissue to repair it through a complex tissue differentiation mechanism.

MSCs could differentiate into several cellular phenotypes, like fibroblast, chondrocyte, myoblast, stromal cells, and osteoblasts; as summarized in this figure, we state in this figure fibroblast, chondrocyte, and osteoblast. But other than these three myoblasts, stromal cells are also formed due to the differentiation of MSCs.

Subsequently, these cells can generate different tissues, like fibrous tissue, cartilage, muscle, marrow, and bone. It has been found that several stimuli, including growth factors, changes in oxygen tension, or hypoxia and mechanical loading, could influence the connective tissue

differentiation. A balance between different stimuli is necessary for facilitating a particular connective tissue differentiation and its growth.

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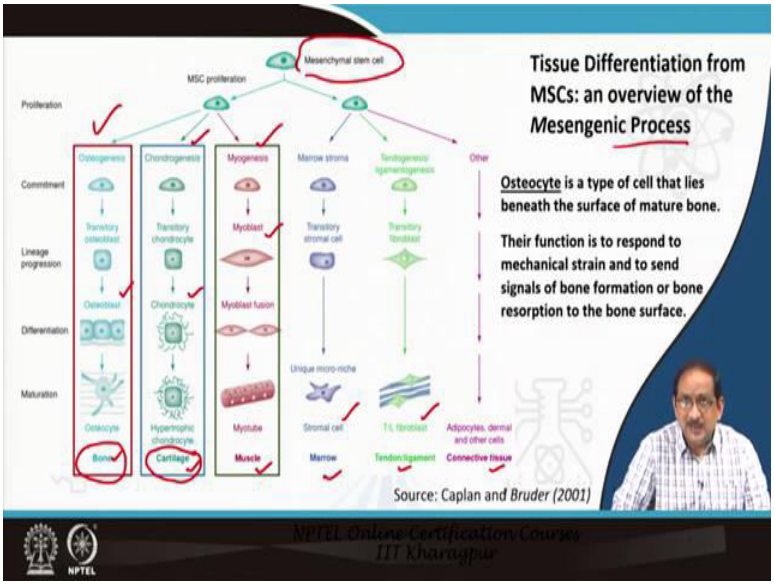

As indicated here, let me present an overview of the mesengenic process of tissue differentiation from MSCs, or mesenchymal stem cells. So, the figure shown here summarizes the tissue differentiation process from the mesenchymal stem cells. MSCs can differentiate into several cellular phenotypes, like osteoblasts, chondrocytes, myoblast, stromal cells, fibroblasts. Subsequently, these cells could generate different tissues, like bone, cartilage, muscle, marrow, fibrous tendon, ligament, and other connective tissues.

Now, the development and formation of bone, as indicated here, is known as osteogenesis. Similarly, the process of development and formation of cartilage from the MSCs is known as chondrogenesis. The other process of development and formation of muscles is known as myogenesis. It may be worth mentioning here that osteocyte is a type of cell that lies beneath the surface of the mature bone; their function is to respond to mechanical strain and to send signals of bone formation, or bone resorption to the bone surface.

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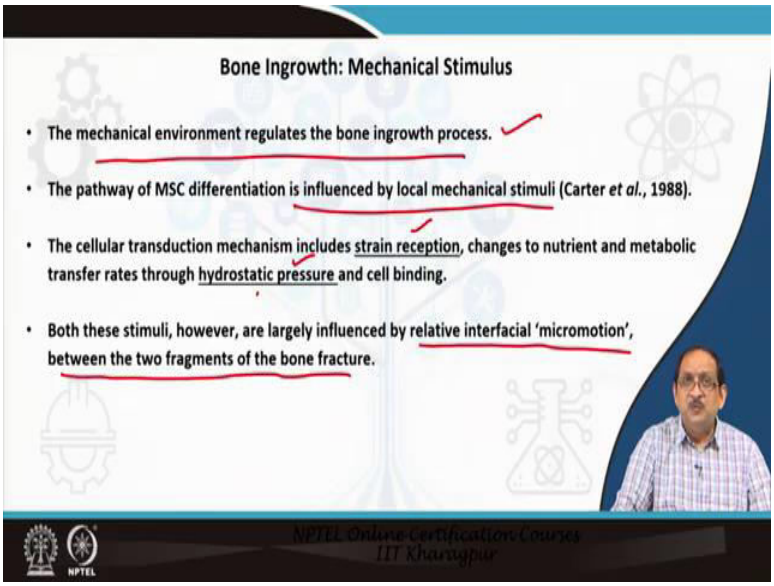

Let us now discuss the mechanical stimulus that is responsible for bone ingrowth. The mechanical environment regulates the process of bone ingrowth. Local mechanical stimuli influence the pathway of MSC differentiation.

The cellular transduction mechanism includes strain reception, changes to nutrient and metabolic transfer rates through hydrostatic pressure and cell binding.

Now, both this stimulus as indicated earlier, strain reception and hydrostatic pressure, however, are primarily influenced by the relative interfacial micromotion, that is, the movement between the two fragmented parts of the bone, which has been fractured. So, it is the relative interfacial micromotion, which means relative movement between two fragments of the fractured bone.

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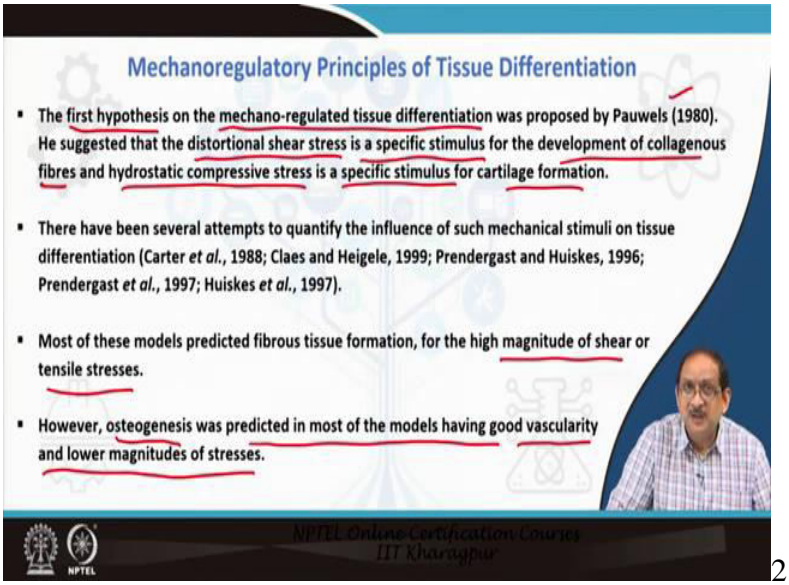
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Now, let us come to the second topic of the lecture, on mechanoregulatory principles of tissue differentiation. The first hypothesis of the mechanoregulated tissue differentiation was proposed by Pauwels in 1980. He suggested that distortional shear stress is a specific stimulus for the development of collagenous fibres and hydrostatic compressive stress is a specific stimulus for cartilage formation.

Over the years, there have been several attempts to quantify the influence of such mechanical stimuli on tissue differentiation. Some of the outstanding contributions are listed here as publications. So, you will find it in the reference list. Most of these models predicted fibrous tissue formation for the high magnitude of shear or tensile stresses.

However, osteogenesis as I indicated earlier, which means formation and development of bone was predicted in most of the models having good vascularity and lower magnitude of stresses, very, very important point to note. So, bone tissue formation is facilitated by blood supply; adequate blood supply is necessary for osteogenesis.

So, osteogenesis was predicted in most models having good vascularity; vascularity means blood supply and lower magnitude of stresses.

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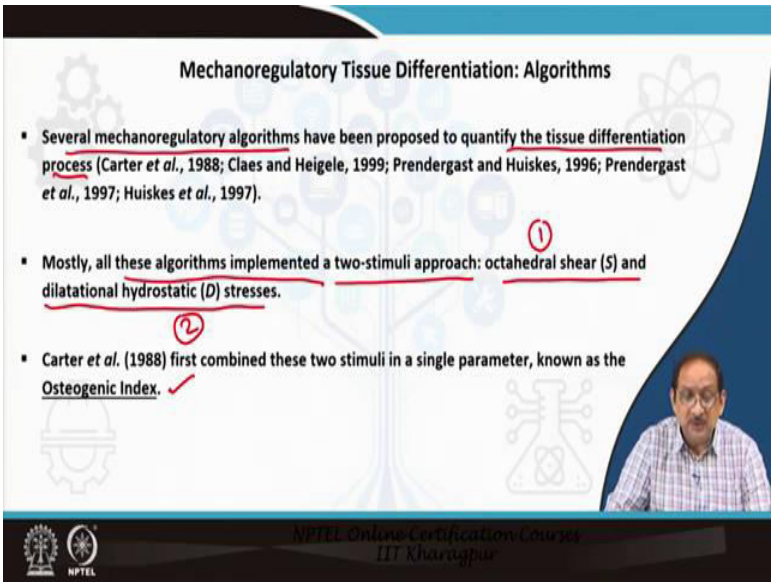

Let us discuss more the algorithms, or the proposed models, by different researchers. Several mechanoregulatory algorithms have been proposed to quantify the tissue differentiation process as indicated here and in the earlier slide. Mostly, all these algorithms implemented a two-stimuli approach based on octahedral shear and dilatational hydrostatic stresses. So, it is based on octahedral shear and dilated dilatational hydrostatic stresses.

Now, Carter, in 1988, first combined these two- stimuli into a single parameter, which was known as the osteogenic index. Although, this osteogenic index approach was developed based on two-dimensional Fe models. The method successfully predicted early tissue differentiation trends for initial fracture fixation and around implant-bone interfaces; there is bone ingrowth around inter bone in interfaces.

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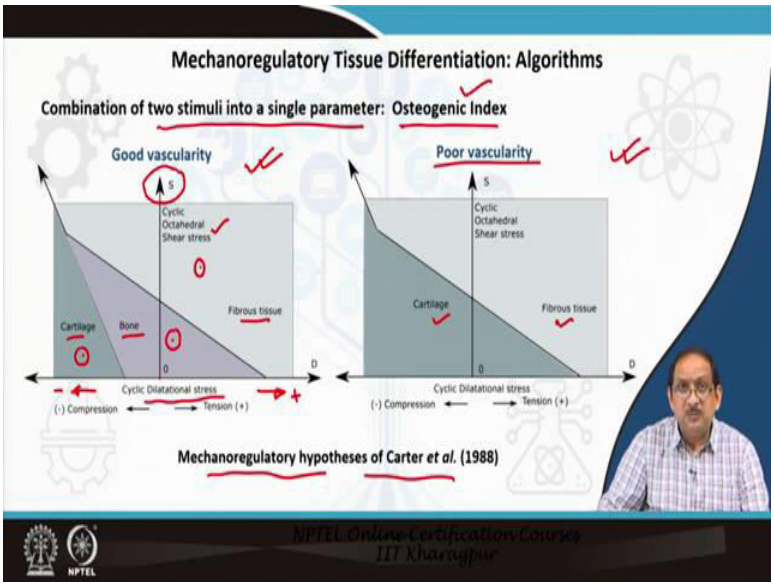

Let us now discuss more in detail the mechanoregulatory hypothesis by Carter in 1988. So, as indicated earlier, the osteogenic index combines two stimuli into a single parameter, as indicated in the slide. Now, we have presented here two figures. Let us first consider the figure on the left, here we see there is two axes. On the x-axis, there is dilatational stress; on the y-axis, we have the octahedral shear stress.

Now, depending on the osteogenic index, we can predict the type of new tissue formed. So, based on the mechanoregulatory hypothesis, the type of tissue, new tissue formed, or new tissue formed can be predicted based on the osteogenic index. So, you can see there are three regions here, fibrous tissue, bone, and cartilage.

Now, if there is the osteogenic index is somewhere here indicated by the point if the osteogenic index value is a point as shown in the figure, then the type of new tissue formed will be fibrous tissue. If the osteogenic index is located somewhere here, within the dark grey region, the formation of bone is predicted. Similarly, if the osteogenic index value is somewhere on the green zone, then cartilage formation is predicted.

Now, this is the 0 point in the graph. So, towards the right from the 0 is tension, and towards the left is compression. So, tensile stresses and compressive stresses are indicated by the positive and negative signs, respectively. On the y axis, you can see, the octahedral shear stresses have been

plotted. Now, this hypothesis is based on the condition that there is good vascularity in the system.

If we move towards the figure on the right, we can see how the hypothesis is changing for the case of poor vascularity. So, there is no zone, which indicates bone tissue formation. So, we have only cartilage formation and fibrous tissue formation indicated in the system, where there is poor vascularity.

So, what can we conclude here? That vascularity is a key factor in osteogenesis, which is the formation of bone tissue, discussed earlier. However, further advancement in the quantitative basis of tissue differentiation suggested that the osteogenic index-based approach becomes less valid with progressive tissue differentiation.

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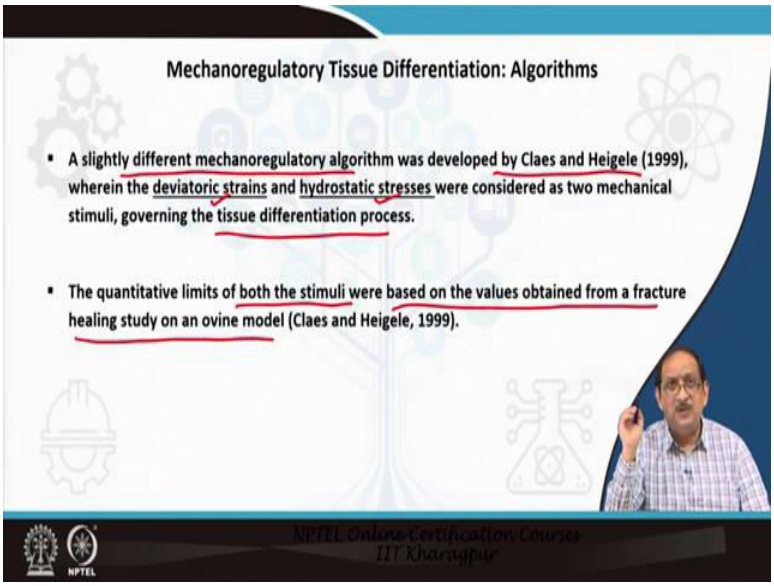

A slightly different mechanoregulatory algorithm was developed by Claes and Heigele in 1999, wherein deviatoric strains and hydrostatic stresses were considered as two mechanical stimuli governing the tissue differentiation process. So, this was another important hypothesis, or algorithm, Claes and Heigele proposed that in 1999. But it was slightly modified as compared to the earlier hypothesis by Carter.

So, we have deviatoric strains and hydrostatic stresses. So, there should be some quantitative limits of both stimuli based on values obtained from a fracture healing study on the ovine model.

So, ovine bone means sheep bone. So, the quantitative limits of both the stimuli were obtained from a fracture healing study on the ovine model or ovine bone model.

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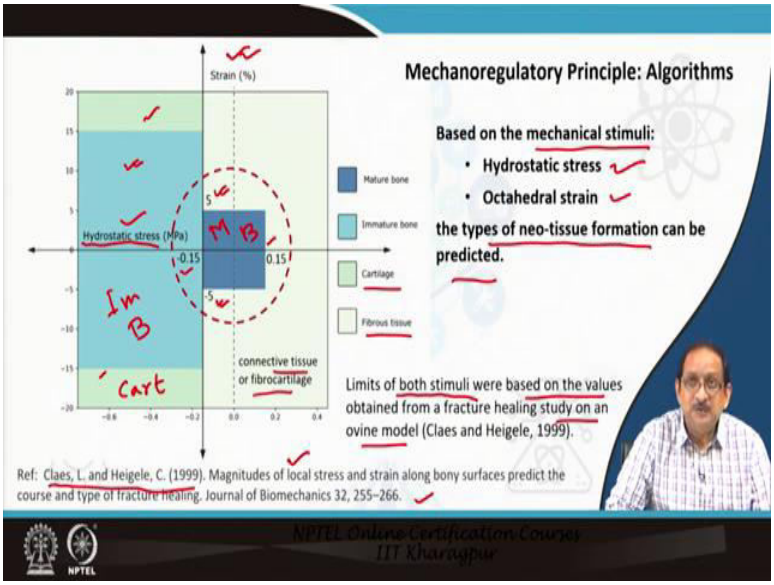

It would be best to concentrate on this slide because the Claes and Heigele hypothesis, or algorithm, is presented. So, based on the mechanical stimuli of hydrostatic stress and octahedral strain. So, we have two axes: the x-axis, both sides hydrostatic stress and the strain on the y axis; based on these two mechanical stimuli, the types of neo-tissue formation can be predicted, or the neo tissue formation can be predicted.

If you look into this figure, we see there are colored zones. So, the very light green is indicated by fibrous tissue as also indicated here in the figure, slightly darker shade of green, we can see the cartilage formation here, the blue color indicates the hypothesis, or the values for which immature bone and mature bone will be formed.

So, the light blue indicates the value of immature bone, and the dark blue zone gives you the values for mature bone, as shown in the figure. Now, you can see that the limits of both stimuli, as I had indicated earlier, were based on values obtained from a fracture healing study on an ovine bone and the limiting values are indicated in the figure.

This hypothesis is based on a very important paper published in 1999 by Claes and Heigele, Magnitudes of local stress and strain along bony surface predict the course and type of fracture healing.

So, this is the paper I would request you to look into the paper for more details. This model of Claes and Heigele presented here was found to predict good tissue differentiation patterns for drilled hole defects.

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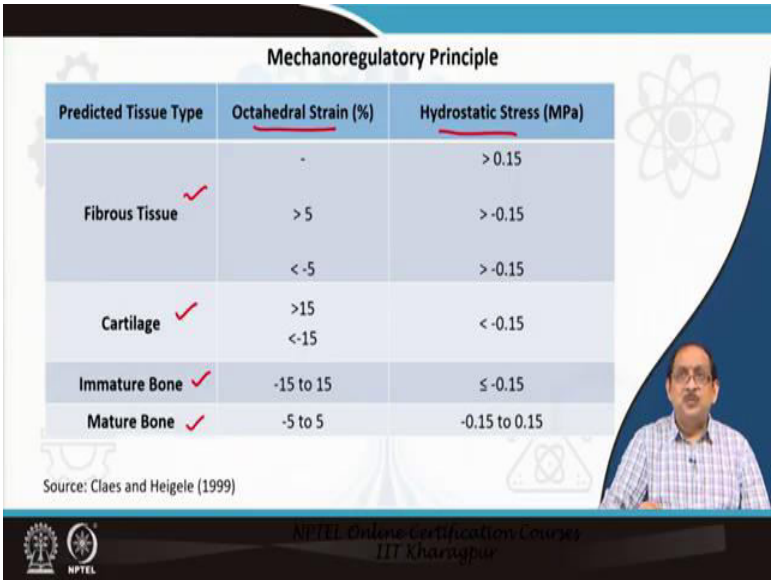

So, based on the discussion in the earlier slide, we have now summarized the predicted tissue types as indicated here, fibrous tissue, cartilage, immature bone, and mature bone, and the mechanical stimulus, octahedral shear strain, and hydrostatic stress. The limiting values are indicated here in the table. So, please have a look in these values and also the paper. I think that would make things more transparent if you would like to know more about the tissue differentiation algorithm proposed by Claes and Heigele.

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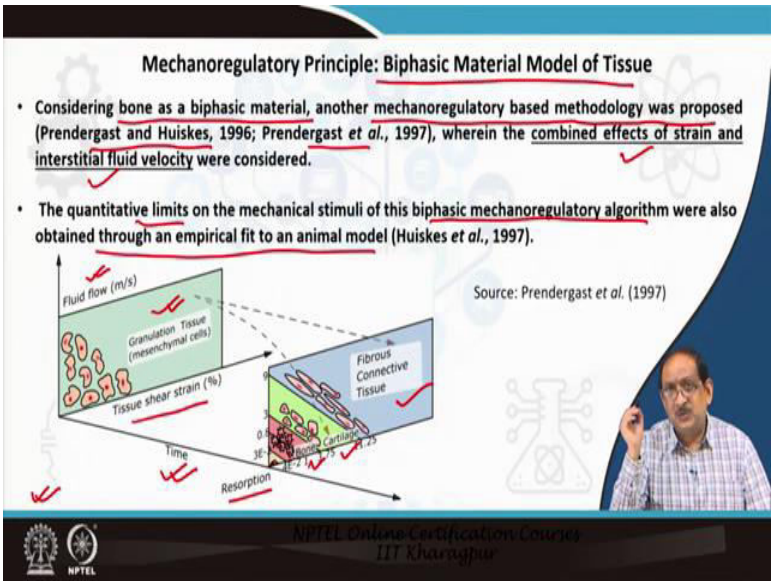

Let us now consider the mechanoregulatory principle applied on a biphasic material model of bone tissue. As discussed earlier, bone can be modelled as a single-phase material, solid material, or it can also be modelled as a biphasic material, consisting of a solid phase and a liquid phase. Now, considering bone as a biphasic material, another mechanoregulatory based methodology or hypothesis was proposed by the Prendergast group with Huiskes, wherein the combined effects of strain and interstitial fluid velocity were considered.

So, combined effects of strain and interstitial fluid velocity were considered. The quantitative limits on the mechanical stimuli of this biphasic algorithm were also obtained through an empirical fit to an animal model. So, the mechanical stimuli consider the combined effects of strain and interstitial fluid velocity in the case of the biphasic material model of bone tissue.

Now, in the figure presented here in the slide, you can see that the tissue shear strain, the tissue shear strain, is plotted along one axis and the fluid flow, another mechanical stimulus is plotted along say y-axis. Now, here we start with granulation tissue, which consists of mesenchymal stem cells and with time, the MSCs differentiate into fibrous connective tissue, cartilage bone, and other types of tissues through the process of evolutionary tissue differentiation. So, as you see in the slide, another term mentioned resorption, which means loss of tissue.

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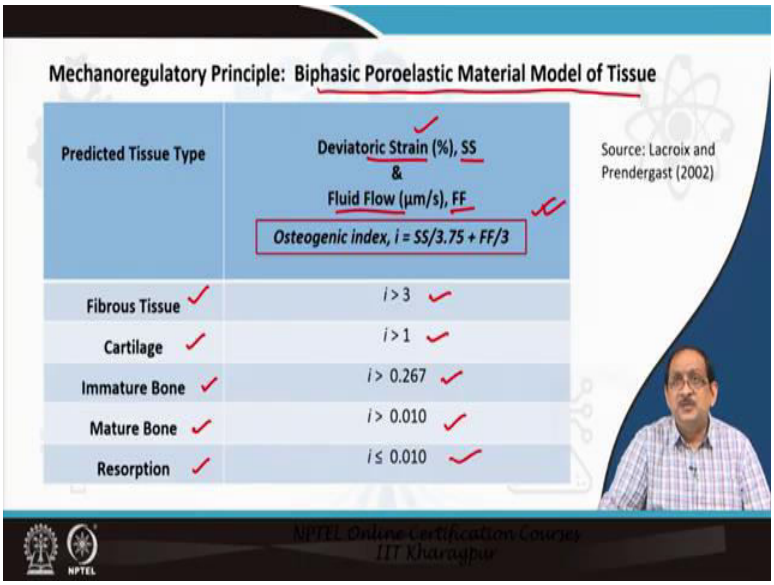

Now, let us present the mechanoregulatory principle, hypothesis, or algorithm for the biphasic poor elastic material model of bone tissue in the tabular form. On the left, there are several predicted tissue types, as you can see from fibrous tissue, cartilage, immature bone, mature bone, and there is another term, resorption, that is loss of bone, resorption means loss of bone.

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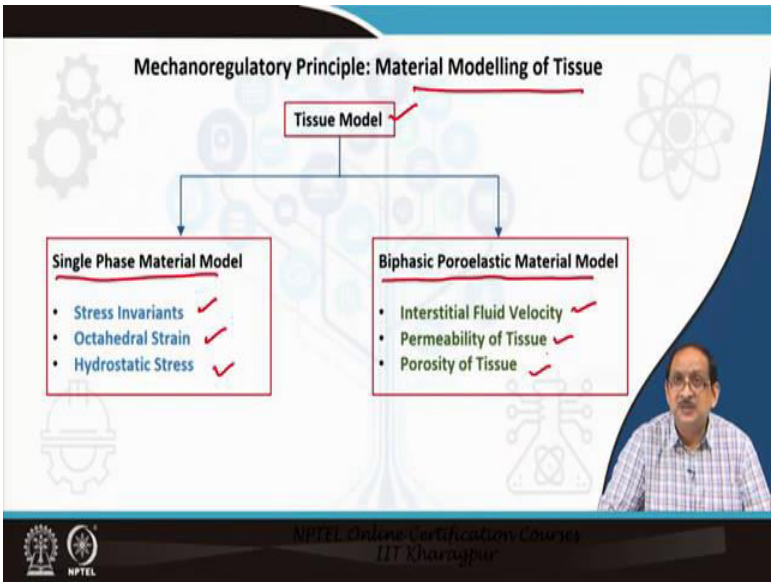

Now, mechanoregulatory principle, as we have discussed already in detail, can differ depending on the material model of the bone tissue. So, if the tissue model is based on a single-phase material model, then the mechanical stimuli will consider stress invariance, octahedral strain, and hydrostatic stress. Whereas, if the tissue model is based on Biphasic Proelastic material, then interstitial fluid velocity, tissue permeability, and porosity of the tissue need to be considered in the mechanical stimuli.

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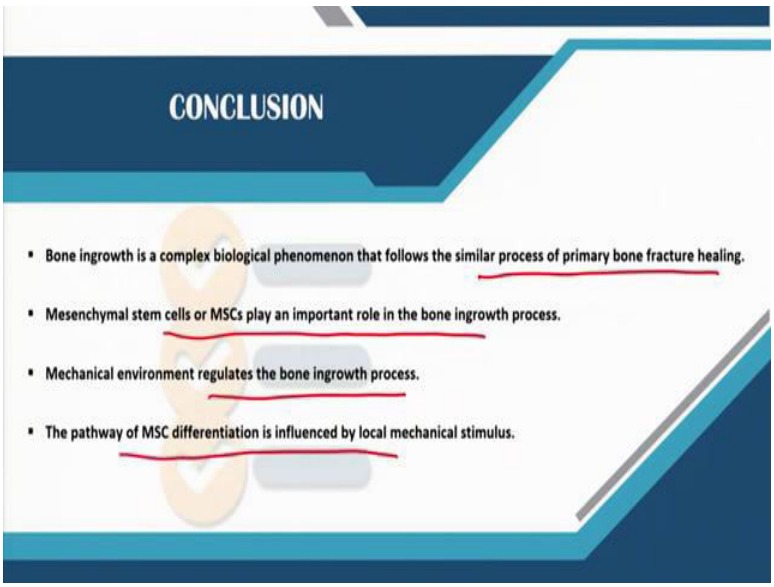

Let us now come to the conclusions of this study. Bone ingrowth is a complex biological phenomenon that follows a similar process of primary bone fracture healing. Mesenchymal stem cells, or MSCs, play an essential role in the bone ingrowth process. The mechanical environment regulates the bone ingrowth process. The local mechanical stimulus influences the pathway of MSC differentiation.

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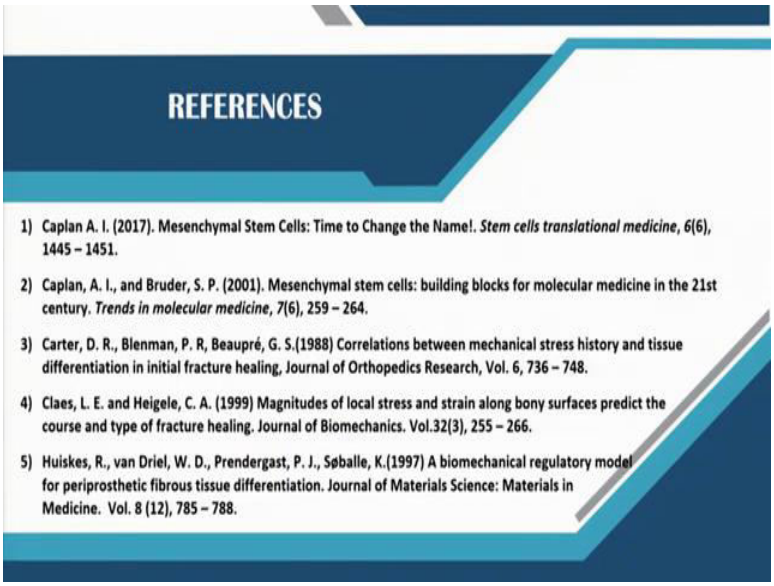

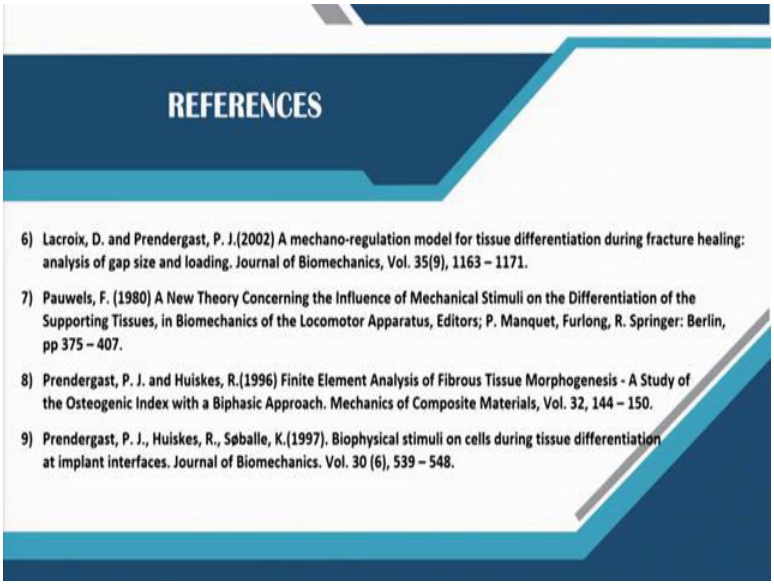

The list of references is indicated in two slides, based on which the lecture has been prepared. And thank you for listening.