Tissue Engineering
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Lecture - 02
Introduction to Tissue Engineering - Part 2

So, today we will continue with our discussion on the Introduction for Tissue Engineering. Yesterday, I had posted a few questions. I hope you had gone back and read a little bit about it.

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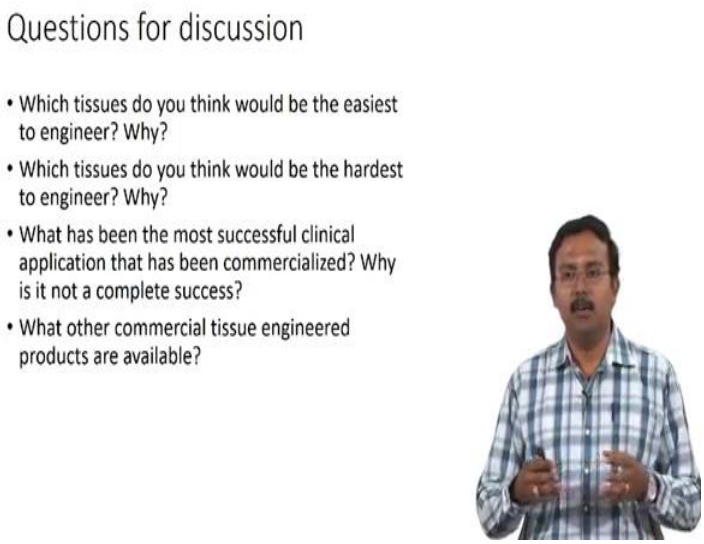

So, we will start with the first question; which tissues do you think would be the easiest to engineer? So, yesterday you answered with a few. Did you find out why you thought those were the easiest? Or did you have a reason for that?

Student: Growing rate, how much time it takes.

That is one good reason. Generally, they regenerate well. So, it might be easier to do, and you had mentioned skin, right ok. So, what else?

Student: Easy to implant.

Ok

So, somebody had also mentioned cartilage. Do you think cartilage regenerates rapidly?

Student: No.

No, then why cartilage? So, what did you identify from the literature?

Student: I thought the function performed would be much simpler than something like maybe heart valves.

Ok

So, functionally cartilage is simpler tissue. Yes, that is one reason why you would think it is easier to emulate that, ok. Any other tissues which you thought off?

Student: No.

So, what about bones?

Student: No, sir.

Bones are also reasonably easier to regenerate compared to most other tissues. So, what do you think is the common factor which you saw between all these tissues? They are just barriers or supports; they are not functional tissues, right. So, the skin is just a barrier; bone is just a supportive tissue; cartilages is also a supportive tissue. All those things are functionally simpler compared to other more complicated tissues. So, which tissues do you think would be harder to engineer?

Heart? Why?

Student: Because of the growth rate is.

Regeneration is very slow. That is one limitation.

Student: Functionality.

The function.

Student: The cells are already highly differentiated.

So, the functionality of heart tissue is very high; Along those lines can you identify other tissues, which would be even harder than a heart tissue?

Student: Nerves, brains.

Nerves and brains ok. So, brain as of now, I do not think anybody is trying to engineer a brain. So, people try to look at nerves and

Student: Lungs.

Like the peripheral nerve system, nerve systems, and things like that.

Lungs ok. So, why? Why do you think it will be harder?

Student: Just asking whether is it harder.

Ok. So?

Student: Lungs are very specialized, right?

Yeah. So, if you are talking about lung as an organ it is very difficult; obviously because of the architecture and there are too many things to consider. But, smaller tissues? Yes, it would be about the same level as hard tissue. It would be the same level of complexity as hard tissue. Think of something which has little more biological functionality?

Student: Pancreas.

Ok. Why pancreas?

Student: Because it is actively performing.

So, the pancreas needs to secrete insulin and glucagon, while it senses the glucose levels, right. So, it has very specific functionality. So, that this is going to make it harder tissue to engineer, so, similarly liver tissue. So, the liver would be another tissue where you would still have similar challenges.

So, these kinds of tissues which have to respond to stimuli are harder to engineer because there are some functionalities which you cannot easily recreate in an in vitro setup, ok.

So, what has been the most successful clinical application that has been commercialized? First, I want you to identify which are all the commercial products that you are able to find.

Student: *inaudible*

I want to know the name of the product.

Student: Dental implant.

Ok, I want to know the name of the product. I want to know what they were, derma graft, ok.

Student: Carticel.

Carticel; carticel is for what tissue?

Student: Cartilage.

derma graft is for skin.

Student: I something called OP1 putty, but I did not know what that was.

What?

Student: It is.

What is it?

Student: Something related to the bone.

OP1 putty?

Student: Yeah.

Ok, I am not aware of it. So, o p. So, just OP number 1?

Student: OP number 1.

Putty ok. So, it is spinal fusion from striker ok. So, basically has a recombinant human bone morphogenetic protein ok. So, what else? Have you seen any other commercial

things? So, the commercial one's kind of align with what you thought would be the easiest tissues to engineer, right. So, another major reason cartilage is actually easier to engineer is because it is avascular tissue. So, you do not need to worry about vasculature. Creating vasculature is one of the limitations in tissue engineering. So, that can actually be overcome when you are working on avascular tissues ok.

So, we have looked at some of the commercialized ones. Actually, the most established commercial product is skin. The first skin, the tissue-engineered product which approved was a skin graft. So, I think it was called Integra. So, the Integra was probably the one commercialized first and approved by FDA. Even with that, it is still not a full success. Can you think of why it is not a full success?

Student: Sense of touch in that area.

Ok, So, that would be one problem because innervation has to happen for the sense of touch, sensory things to have be there. That is one thing. So, what else?

Student: It is not yet fully biocompatible.

Ok, why do you think that is the case?

Student: Maybe due to immune reactions.

So, dermagraft; Ramya you identified dermagraft, right? Do you know what it is made of?

Student: I did not write it down.

Ok. So, it basically has a matrix on which cells are seeded. It is not an acellular thing. So, it already contains some cells from other sources, which can cause immunological reactions. There are acellular tissues as well, which are used. So, I think MatriDerm is probably one product where you use an acellular matrix which does not have cells with it. Even with all that, your reinnervation is one thing, your sweat glands and this perspiration is one thing, where aesthetic aspects where you have the hair growth or matching the skin tone of the person, all these things can be a challenge.

So, because of these things, it is not a complete success. However, it has been reasonably successful in providing enough of a healing effect. And another major limitation you

would see with most of these things are they are ridiculously expensive. It is not like; it can easily and readily be used by everybody for general use.

So, we already labeled and identified a few other commercial tissue-engineered products, and all of them have their own limitations. One major limitation is the size of the tissue-engineered construct itself which is because of the vascularization or the lack thereof; which leads to very little nutrient supply or its supply has to come only through diffusion, and that is not the most efficient way for nutrient supply or toxin removal ok. So, let's move on.

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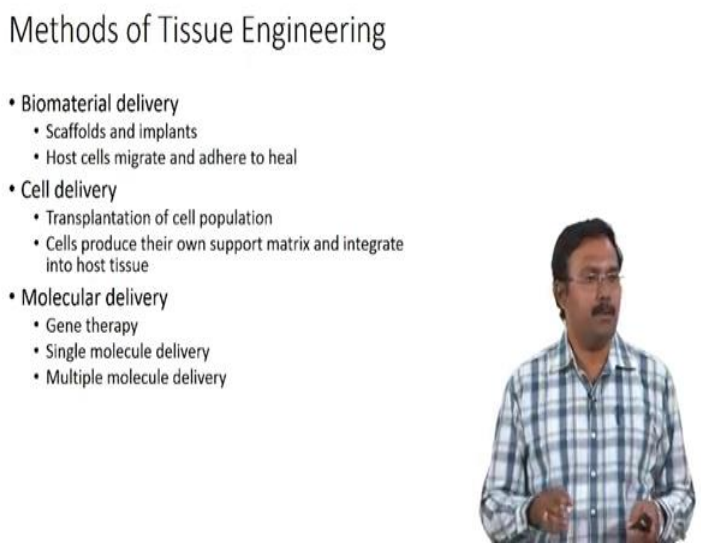

Currently, there are different ways to engineer tissues. I have segregated them, but as of now, people do not try to do them independently. People try to prepare combinations. As I had already discussed the tissue engineering triad, it follows the same pattern. You could either use material or cells or molecules which can trigger the regeneration of tissues.

So, biomaterial delivery is where you use scaffolds or implants, and the host cells will have to migrate here, adhere to the material, and help in the healing process. People use cell delivery as well, where you use transplantation of the cell population. The cells will basically produce their own support matrix and integrate into host tissue. So, this is where you have the stem cell therapy and all other things where you just harvest stem cells and supply it to the site of injury, hoping it will help in the regeneration.

So, those kinds of things are done for cell therapy, and you also can have molecular delivery, where you either use gene delivery or single molecule or multiple molecule delivery. The product which Ramya identified what is it? OP1 putty, right. So, that is recombinant bone morphogenetic protein. So, bone morphogenetic protein is a growth factor which helps in the formation of bones.

So, delivering such a molecule would help in the regeneration of the tissue. Currently, people focus on combining these things. So, people have seen that using them independently has its own advantages, but it can only help in regeneration to a certain extent. Beyond that point, you need to have multifunctional material which can provide different avenues for regeneration itself.

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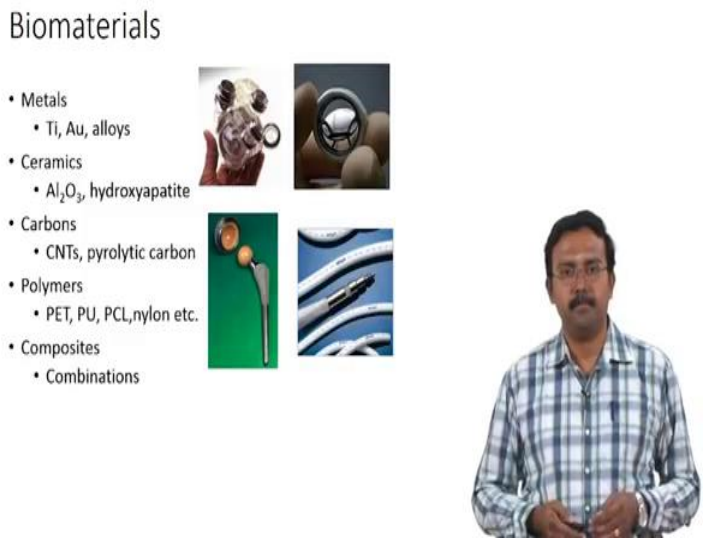

So, the materials which are used can be classified primarily as four things. So, they are metals, ceramics, carbons, and polymers. Metals are basically titanium, gold, silver, and alloys. Ceramics; it can be alumina, zirconia, hydroxyapatite. So many different ceramics are available. You have the carbons, which would be carbon nanotubes, pyrolytic carbons, graphene, fullerenes.

There are too many options where you can try to use them. So, people have been trying to use these for different biomedical applications. Polymer, obviously there is a wide array. Whatever I have listed here is only synthetic polymers. You can also use natural polymers like chitosan, collagen. There is just a wide array of options which can be used.

So, these are the four major classes of biomaterials and composite is just another class which is basically a combination of these materials, which we have said. People use polymers along with ceramics or carbons and to provide different functionality. We will go into a little bit of detail of all these things, and hopefully, we will have more discussion in the subsequent lectures.

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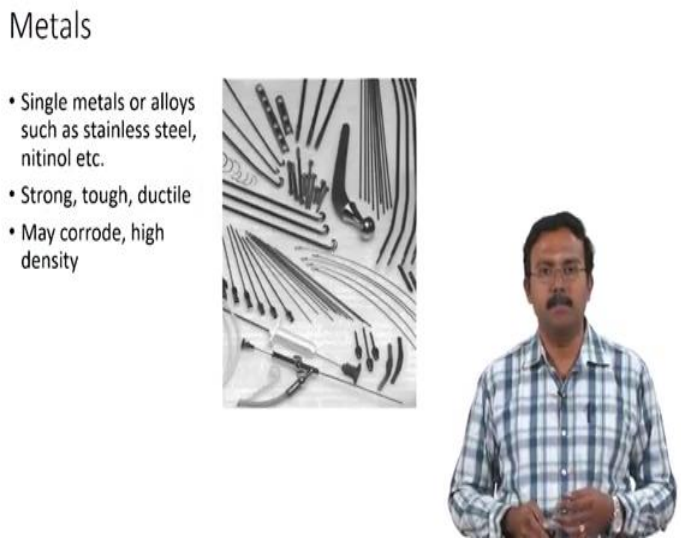

So, metals can either be a single metal or alloy. Some examples for alloys which are used in the biomedical application would be stainless steel and nitinol. The advantages: they are strong, tough, and ductile; however, the disadvantages are; they may corrode, and they usually have very high density. So, this would mean there could be discomfort for a patient when it is being implanted in the body. So, that could be a limitation.

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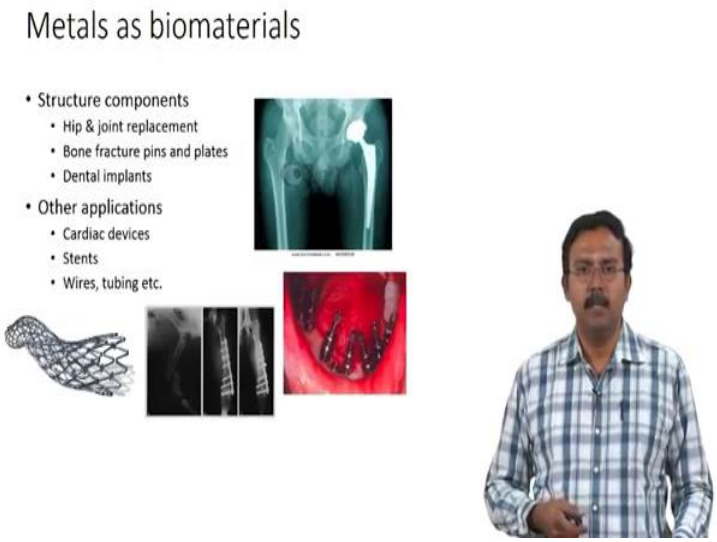

So, metals are used as biomaterials in many cases. Some of the options are where you use it for structural components like hip and joint replacements, bone fracture pins, and plates which is used during surgery; you also have dental implants where metals are used. So, other applications would be for cardiac devices, stents, wires, and tubing. So, what you see here this is actually a stent.

This is how stent looks, and this is used to make sure the blood vessels do not collapse. So, in the case of angioplasty, that is what is done. So, you actually put the stent there, and it helps to keep the blood vessel open.

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And nitinol is one alloy which is quite popular. How many of you know what nitinol is? Does anybody know what nitinol is? So, this is a superelastic material which is used in vascular stents. Hope this video plays ok. Let's see if it plays ok.

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I really did not want the audio. So, that is just a water bath you are looking at. So, what you have here is just a water bath and the wire which they are playing with is the nitinol wire. So, any kind of deformation it will again go back to its shape provided the environment is right. Like temperature and the physiological conditions, it will actually

go back to its original shape. It is called as the shape memory alloy. It can retain shape and elasticity. This can be deformed for easy implantation. So, you do not have to open up the patient all the way to put this in. And it restores its original shape inside the body. So, that is why in angioplasty; all they do is just have basically catheter which is put inside the person body either through the wrist or through some blood vessels between the thighs. It is a simple enough procedure because the material can actually be deformed and it will regain its original shape once it is implanted.

So, people are now looking at developing these stents for different applications. Recently, there was an FDA approval for even bifurcation stents. So, when there is a clog in the blood vessel, a stent is placed, so that the vessel can be kept open. But what can happen is these kinds of clog can happen at the point of bifurcation of blood vessels? If that happens, keeping one stent is not sufficient. So, what people trying to do is they put one, cut it open and place another. It is actually a very cumbersome procedure to do. So now, there has been some approvals which have come out for bifurcation stents. Some approvals had already been obtained in the European Union, but recently it was approved in FDA as well.

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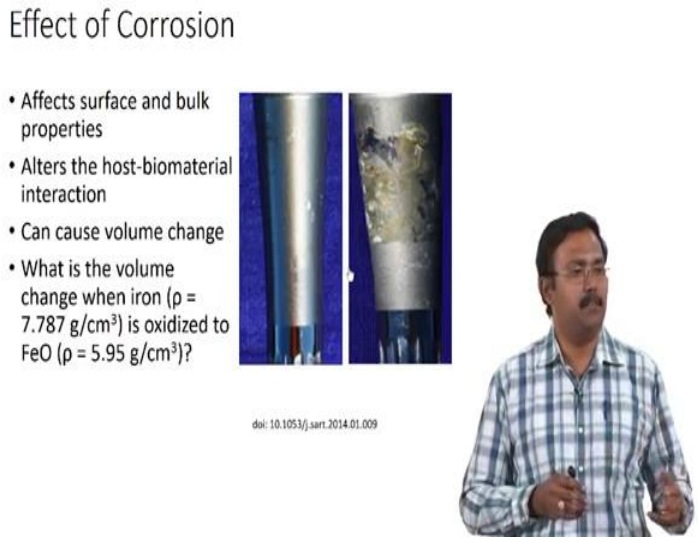

So, the major problem with metallic implants is the effect of corrosion. This would affect the surface and bulk properties. It also alters the way the material interacts with the host because you now have a different surface morphology and even the chemistry is

different. You do not know how the cells are going to react to it. So, it can cause problems. It can also cause serious volume change.

So, if you are going to use something like iron, obviously, you would not use iron. You would use stainless steel or something, but there is going to be a significant change in density. When you have some corrosion and if the density for iron is 7.8 roughly and the iron oxide is close to 6, you have a significant difference in volume which you are going to have, and this will cause major discomfort for a patient.

The image you see here is actually a new implant for hip and joint replacement. The one on the left side is the actual new implant, and the other one is basically taken out from a patient after a few years. So, you can see there is some amount of corrosion, and this can actually be a problem.

So, that is one of the reasons metals are usually an issue, and that is why people use very specific metals which can prevent this kind of corrosion. This image shown here is actually of titanium. So, titanium is one of the most stable materials, and even with that, you have this kind of a problem.

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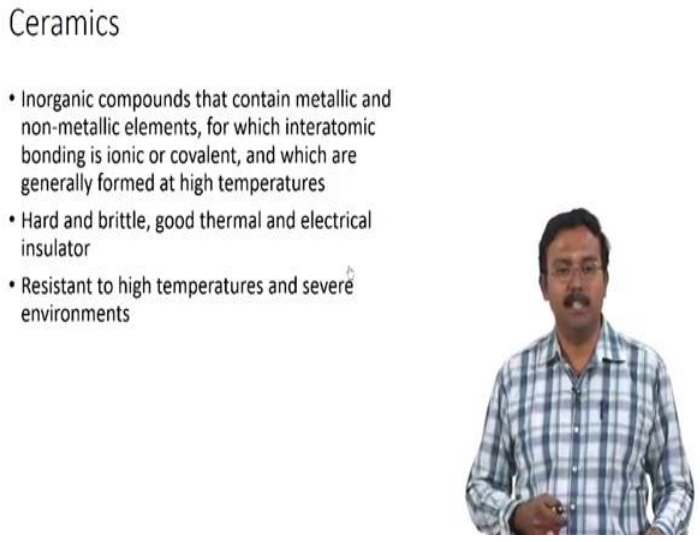

So, ceramics are basically inorganic compounds that contain metallic and non-metallic elements for which you have inter-atomic bonding which can either be ionic or covalent.

These are generally formed at very high temperatures. So, a glass mug, a mug you use would be ceramic, right.

So, these are hard and brittle. They are very hard, but they break very easily. They have good thermal and electrical resistance; they are good insulators, they are also resistant to high temperature and severe environments. Ceramics used in biomedical applications. Where do you think ceramics can be used widely? Which tissue would you want to use?

Student: Bones.

Bones and dental tissues are where you use ceramics because that is where you have ceramics in your body.

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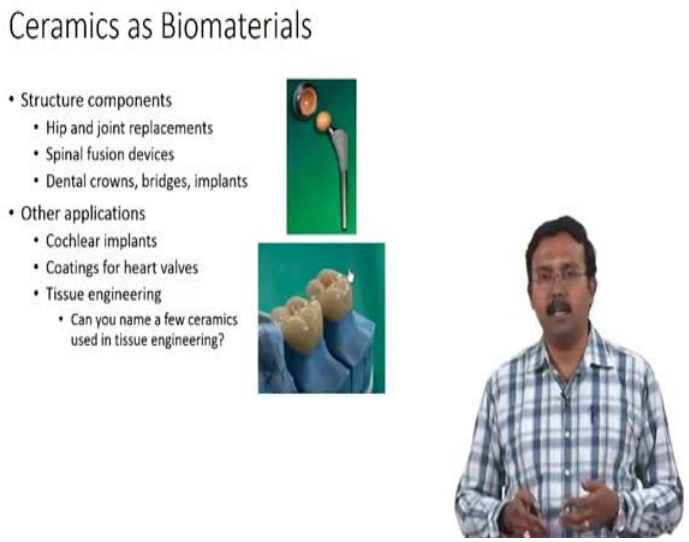

So, it is used in structural components like hip and joint replacements. You do not use the ceramic entirely for joint replacements, because as I said they are brittle. So, you would not want to place only a ceramic there, but it is used as a coating, or it is used in ways that it can help in cell infiltration and so on. Spinal fusion devices can also be ceramic materials and dental crowns which are commonly used.

If you undergo something like a root canal, you would have to get a dental crown, and that would use ceramics and also metals. That is what people used to use earlier. Now to make sure it fits with what you already have, people use ceramics. Other applications

would be cochlear implants, coatings on heart valves. So, in tissue engineering can you name any ceramic which is used?

Student: Hydroxyapatite.

So why, hydroxyapatite?

Student: Because it is part of the bone already.

Ok, So, your bone tissue contains hydroxyapatite. Your bone actually has two components. So, one is hydroxyapatite, which is in the nanoparticle size, and this hydroxyapatite is actually the discontinuous phase. The continuous phase is collagen. So, collagen with hydroxyapatite composite is what your bone is made up off. So, that is why it is a nanocomposite. Bone is actually a nanocomposite material.

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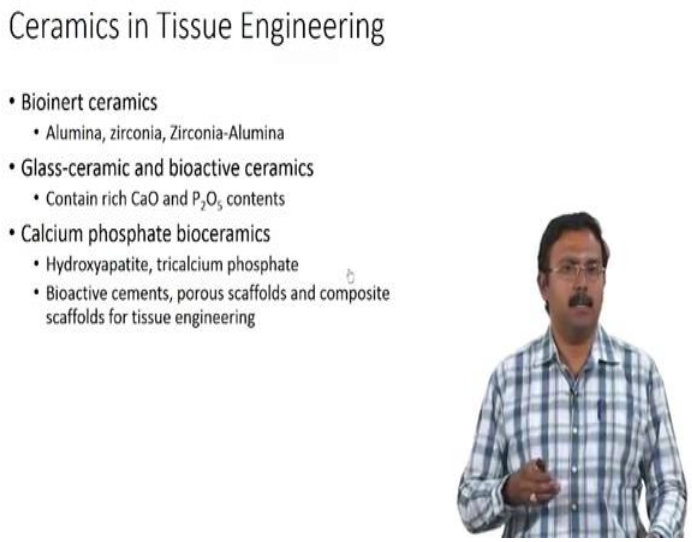

Some of the ceramics which are used are alumina, zirconia, zirconia-alumina complexes. So, these are bio-inert ceramics. bio-inert ceramics would not promote bone in-growth. You can have bio-active ceramics, which are the hydroxyapatite and tricalcium phosphate and so on which will promote bone in-growth. So, there are different types of calcium phosphate bio-ceramics. Hydroxyapatite is a one which has the calcium to phosphate ratio closest to the one in your bones. So, that is why hydroxyapatite is extensively studied for bone tissue engineering.

So, tricalcium phosphate can also be used. You can actually tailor the degradation rates by using different types of tricalcium phosphate. So, that is why people try to use that as well. So, people are using bio-active cement and porous scaffolds and composite scaffolds for tissue engineering. So, people also try to emulate what they have seen in the body. People try to use polymers along with ceramics so that they can actually create bone-like tissues.

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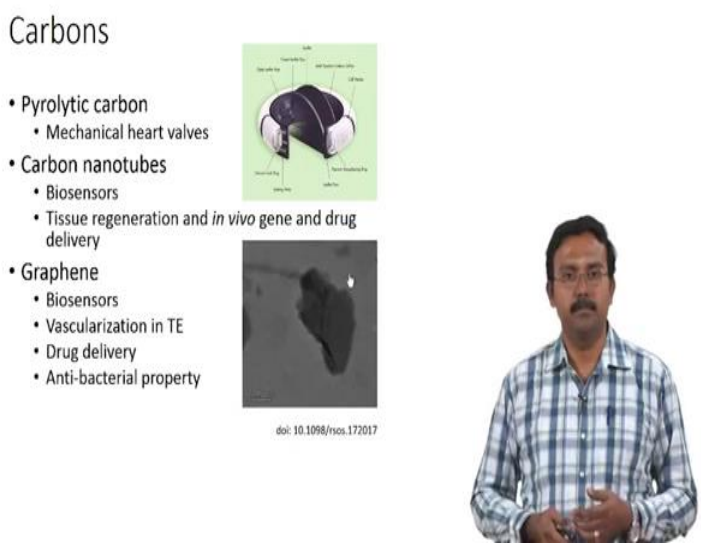

So, carbons are basically just different types; different allotropes of carbon can be used. Pyrolytic carbon is used as a coating for mechanical heart valves. Diamond-like carbon is also used for coating on heart valves and blood contact devices because diamond-like carbon has very good haemocompatibility. So, you use it for coating on blood contact surfaces. Carbon nanotubes also had a lot of interest in the last couple of decades, probably.

So, it is being used for bio-sensors, bone regeneration and other gene and drug delivery applications and so on. Recently, graphene and graphene-based compounds are also used. So, graphene, graphene oxide, reduced graphene oxide, all these things are being explored. The image you see here is actually a TEM image of reduced graphene oxide. This is used in bio-sensors and also for drug delivery applications, and it has very good antibacterial properties. So, it is being explored for coating on implants and so on.

Recent studies have also shown that at certain concentrations these graphene oxides and reduced graphene oxides can help in vascularization, whereas at higher concentrations, they will inhibit angiogenesis. So, you can use it at a different concentration. If you use it at higher concentration, you can probably use it for treating cancers, while if you use it in lower concentration, you might be able to use it for promoting angiogenesis in tissue engineering.

So, most of these carbons there are a lot of detractors for it; because people are worried about the long-term effects. There are very few studies on the long-term toxicities of such carbons because these are nanoparticles and toxicology of nanoparticles itself is a major question mark which is being explored.

So, this being a carbon which is not established for a long time, raises serious red flags in many cases. However, the promise which these materials are showing has made it an interesting material to work on. There is a lot of research which is happening in this domain.

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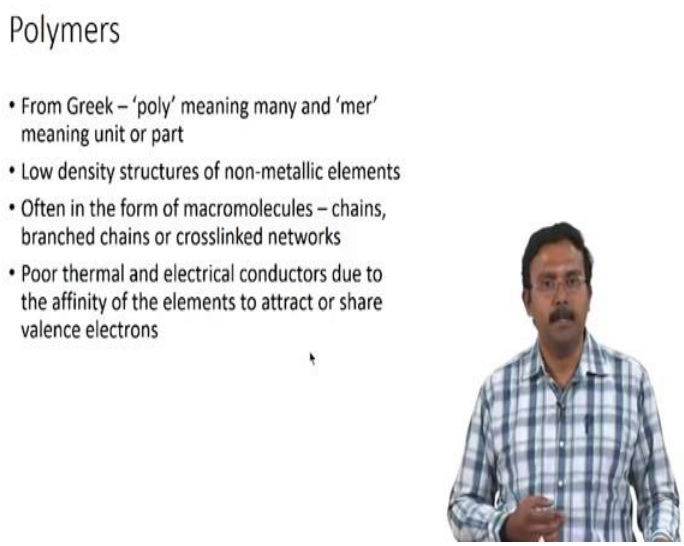

So, moving to the polymers. So, this is where I work. Most of my lab students work on polymers. We try to develop different types of polymers and polymer composites for various applications; either it could be for an implant application or drug delivery application or tissue engineering application. Here which type of polymer material you

use; would be driven by the tissue you are trying to regenerate. You try to design polymers in a way that it will be similar to the natural tissue itself.

So, these things I am assuming you already know. Poly is many, mer is the unit. A polymer is basically a repeating unit. So, these are non-metallic components which form macromolecules. It could be chains, branched chains, or crosslinked networks. They have poor thermal and electrical conductivity. However, there are some conducting polymers as well, which have been used for nerve tissue engineering and so on.

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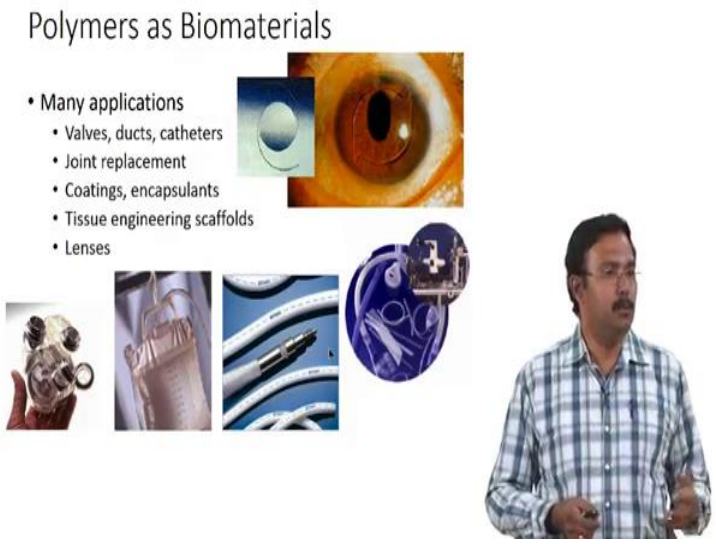

Polymers are one of the most widely used biomaterials. There are just too many types of polymers. Each polymer has its own property; physical, chemical, and biological properties. They are so vast, and it has been used in all possible applications; valves, ducts, catheters, joint replacements, extrusion coatings, encapsulants, tissue engineering scaffolds, lenses. From anything from blood bag to the tissue-engineered scaffold, you are looking at using a polymer.

So, there are just a wide array of applications that you can look at, and depending on the application; you would be looking for very different properties. See if you are going to use it as a lens, what would be the property of the lens for your eye? What would be the property to focus on?

Student: Has be transparent; transparent.

Transparent. So, what about if it is going to be used as a blood bag?

Student: It should not affect the blood inside.

Ok. So, it should not trigger coagulation cascades, right. Which means it should be hemocompatible (i.e.), it needs to be blood compatible. So, the platelet pathway should not get activated. Platelet should not start adhering and initiate clotting. If that happens, the blood will be unusable. So, each material has to be uniquely different, and people try to engineer these materials. We try to modify surfaces to provide desirable properties.

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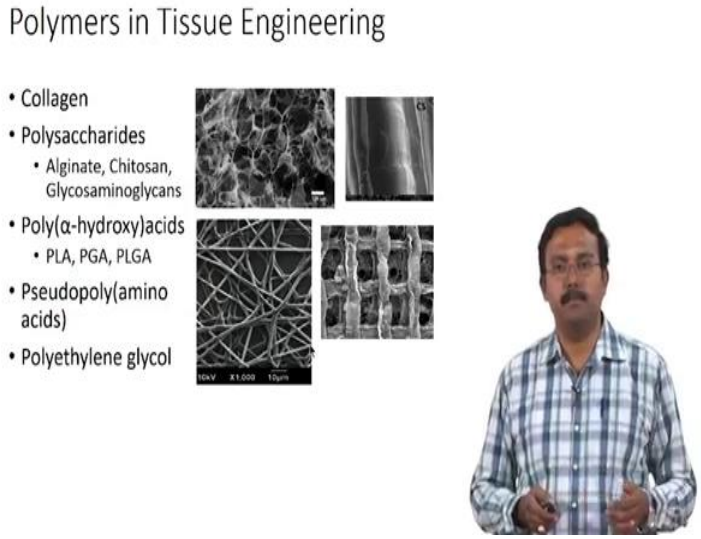

So, PMMA is used there, and mostly people do not use polymers by themselves. It will again be used with other combinations, with ceramics and so on. Collagen is the gold standard because that is what is present in your body. So, you have collagen as the major component of your extracellular matrix (ECM).

So, people try to use collagen. However, collagen can be expensive if you are going to get it as highly purified form. You could try to extract collagen from other sources. We can get it from any source right; any tissue would contain collagen. So, if you were to take just chicken skin and you start treating and perform the proper procedure, you can actually extract the collagen.

However, collagen is not the only material you want to use. People are trying to look at different things; because when you talk about natural materials, you can always have a

batch to batch variations, and there is also the risk of contamination. So, considering all those reasons, people try to use other sources.

Polysaccharides are natural sources. You also have PLA, PLGA, PVA or PEG and so many other materials which you can use. All these things that are synthetic materials, where you have very good control over the molecular weight, which means the physical properties can also be controlled very well.

So, we will try to use so many different materials, and these materials are also fabricated differently. What you see here are different fabrication techniques. The first one you see is probably just a lyophilization and freeze-drying or freeze-thawing technique, which creates a lot of pores.

And the next one you see is just a solvent casting technique where you have something like a hydrogel, smooth surface hydrogel and the one you see after is actually the electrospinning, where you get nice fibers which could be of nano diameters.

And the next one is more like a printing where you get molding, where you get specific structures. So, there are just many fabrication techniques. We will go into the details of the fabrication techniques when we talk about individual materials.

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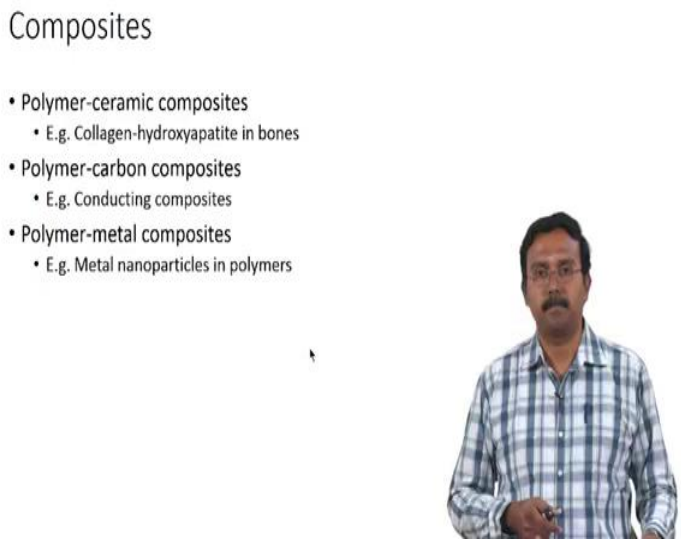

So, composites can be anything. Composites are basically polymers and ceramics put together. Collagen hydroxyapatite is a composite in bones, and you can have polymers

and carbons combining to form conducting composites. So, people have looked at putting a polymer like PCU along with graphene to show whether it can improve the electrical properties. Polymers can also be blended with metals like metal nanoparticles to provide the antibacterial property or to deliver drugs and so on.

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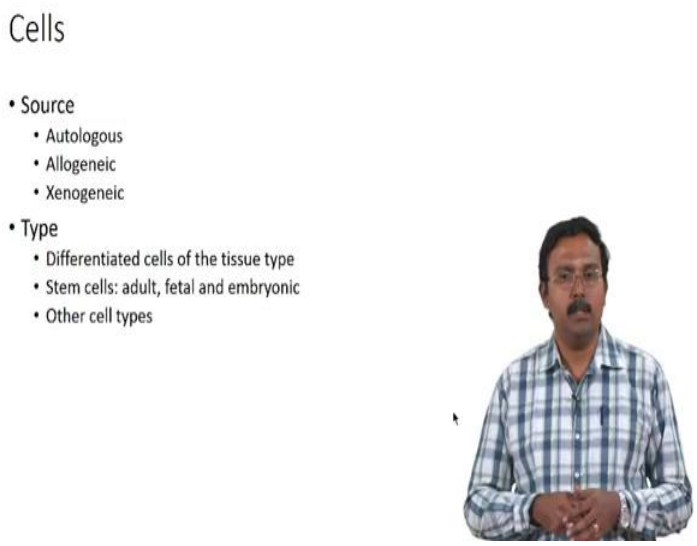

So, that covers the aspects related to materials. You also have cells which can be delivered. So, that is the next part of this work. How do you deliver cells? What cells do you choose to deliver? So, again, it depends on the cell source and cell types. Cells can come from different sources. It can also be of different types. So, we need to identify what cell source we want, to use for it for a specific application and what would be the cell type you would want to use for the specific applications.

The sources I have classified as autologous, allogeneic, xenogeneic and types; I have classified them as differentiated and stem cells and just put other types of cells, where you can use a cell type which is not directly related to the tissue you are looking at, or you can look at co-culturing and so on. So, let’s look at these cell sources first. What do you think could be the advantage of using an autologous cell?

Student: Less immune response.

No, the immune response is from your own body. So, there is no chance of any immune response. Ok. What would be the disadvantage of using an autologous cell?

Student: Invasive procedure.

Ok. Invasive. Sorry?

Student: Limited amount.

Limited amount ok.

Student: It causes problems in the tissues like the location you are extracting.

So, that is called Donor Site Morbidity. Basically, you are damaging another tissue to harvest the cells, and if a patient is already suffering, creating another damage to the tissue would be a problem. So, what about the allogeneic transplant, allogeneic cells? What would be the advantage of allogeneic cells? Allogeneic is from the same species, some other person? So, what would be the advantage?

Student: Abundance and higher availability.

Abundance Ok, sorry higher?

Student: Higher availability.

So, it is more easily available. Disadvantages should be?

Student: Immune responses.

Potential immune responses and rejections would be a limitation. What about xenogeneic; from another species?

Student: Readily available.

So, much easier availability, right. So, if you are going to get tissues from an animal, you are probably going to get more of it, and it is much easier to get animal tissues compared to human tissues, right. So, ethically also it is a little easier to justify doing something like that. So, what about the limitation itself?

Student: Rejection.

Rejection would be the major problem, right.

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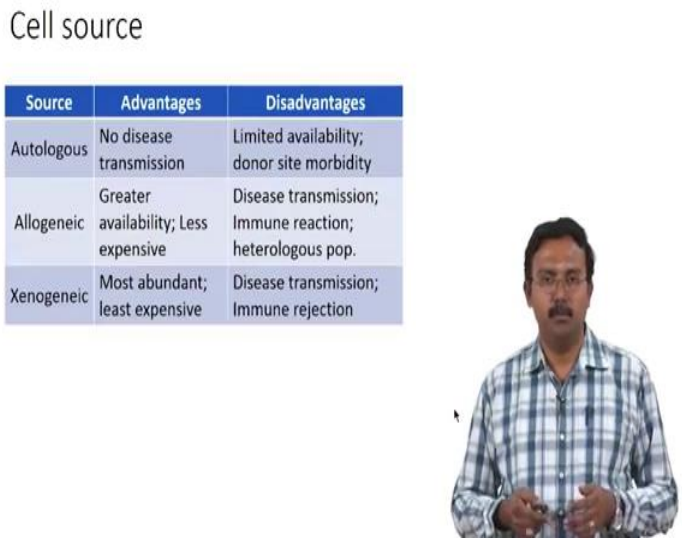

So, that is what I have here. Basically, you have limitations with all these techniques. So, you need to look at how you would optimize it. People try to work on these; people try to develop technologies so that they can expand cells. You can only harvest a certain number of cells, right. You cannot harvest all the cells you need for creating a tissue.

You harvest some number of cells, and then you grow the cells. You provide the right environment, right nutrients so that the cells grow and then you can use this cell population for regeneration. So, that is what people try to do, and because of this, people have developed different technologies for different types of cell, and people are working on next improving this further. So, what about cell types? I said differentiated cells and stem cells, what do you think would be an advantage of using a differentiated cell?

Student: If it is the functional tissue which we are making, then we will know that is the tissue which is going to be, and that is the cell, which will be there.

So, you know that the functionality is already there. So, that is one advantage. Just a tissue is already a functional tissue. What would be the disadvantage?

Student: Differentiated cells do not divide. So, difficult in growing.

So, they will be very slow in growing. You would not be able to get enough numbers. So, that can actually be a major limitation. What about stem cells? So, stem cells actually, can be from different sources. It can be from adults, from fetuses or they can be

embryonic, and you also have IPSCs now. Ok. So, there are different types of stem cells which are available. We will go into details of each of them later, but right now, what would be an advantage of using stem cells?

Student: You can differentiate it into any type of cells.

Ok. So, you can provide the functionality you want, ok.

Student: It is abundant.

Much more abundant and easier to harvest, and they will divide faster. They will grow at a much faster rate making it easier to culture them. What would be the disadvantage of using a stem cell?

Student: You have to provide the right factors for it to differentiate.

Ok. So, controlling the differentiation of stem cells can be a challenge, especially in vivo. So, in vitro differentiation is one thing, but if you are going to use a stem cell and you are going to use it in vivo if you are going to implant it as a stem cell, how do you control the differentiation of the stem cells in vivo? So, that becomes a different kind of a challenge. So, what else?

Student: Cancer.

Can you explain it? What you are saying is correct but?

Student: Like unregulated growth rate.

Uncontrolled growth can lead to teratoma formations, especially with respect to embryonic stem cells. That is a problem. You can actually have that issue where it forms into a teratoma, and that can be a whole new complication you have developed now.

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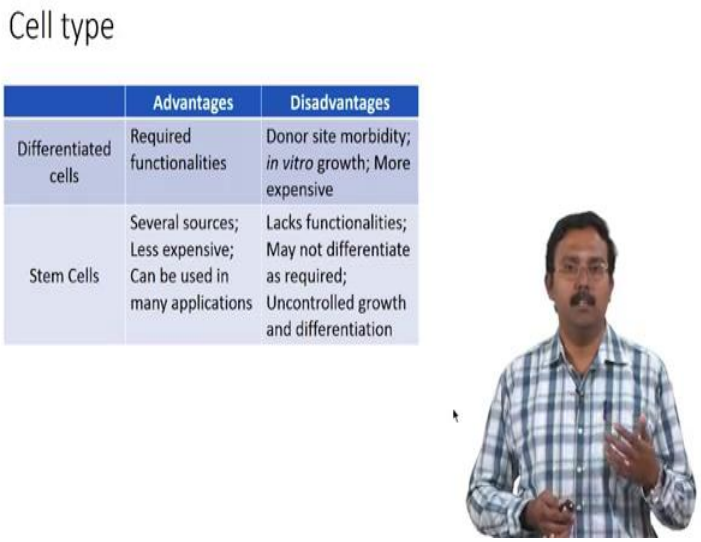

So, that is what I have here. You have required functionalities with differentiated cells, but stem cells can give you different functionalities, can actually be differentiated to specific functionalities, but how you differentiate them in vivo is a challenge.

You have to take into consideration all these things while you are developing your product or the problem statement. So, as far as your project goes, do not just use stem cell because it just sounds cooler ok. You would have to justify why you would want to use a stem cell for this application? If you are going to work on something, make sure you have a strong reason to do this.

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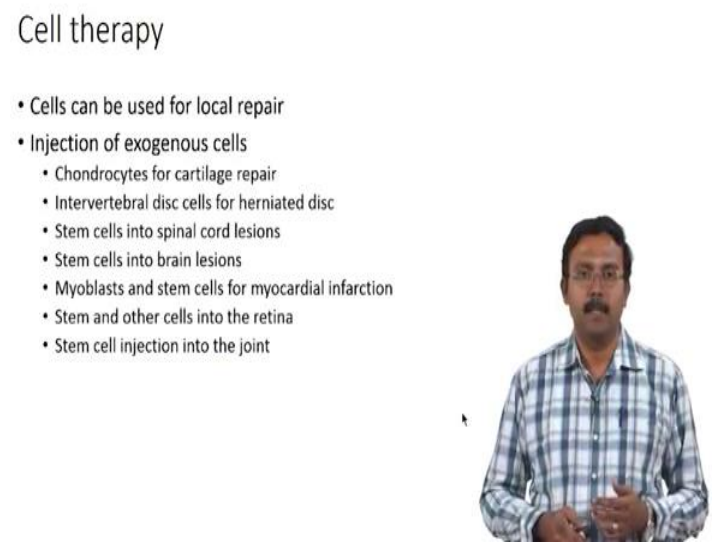

Cell therapy; there are different types of cell therapies which are done even today. So, people use it for local repair of tissues. Injection of exogenous cells, especially chondrocytes for cartilage repair, disc cells for herniated disc, stem cells treatment for spinal cord lesions and brain lesions, are all commonly done. People also look at injecting myoblasts and stem cells for treating myocardial infarction.

Cells for regenerating retina and joints are all stem cell therapies, which have all been explored. Some of them are experimental; some of them have been reasonably established, although there might not be enough of case studies or like a proper clinical study to prove its efficacy.

Some of them have that, many of them may not. So, you might just have doctors taking cells and injecting it. Basically, it has a lot of growth factors when you draw some blood or anything. It will have other factors which will help in regeneration anyways, and people try to see that will be effective.

So, one example would be platelet-rich plasma therapy or platelet-poor plasma therapy. All they do is, take the blood out and spin it out to get the plasma and this plasma either with platelets or without platelets or like with very little platelets can be injected to damaged tissues, and people have seen that this helps in faster regeneration. That is because plasma has growth factors, and you have all the signaling molecules which will probably trigger some kind of healing mechanism. So, people have shown such things.

So, one of the major places where cell therapy has been quite successful and has been studied reasonably well for a long period of time is chondrocyte implants for cartilage repair.

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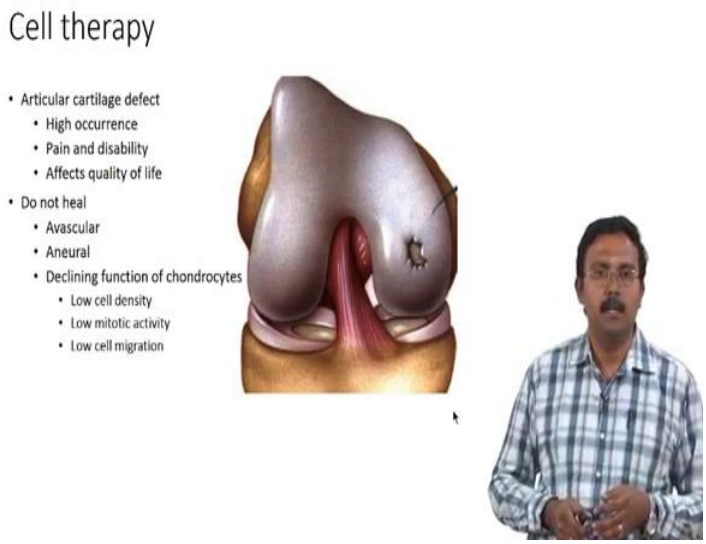

So, we will look at that as an example. What you see here is an articular cartilage defect. How many of you know what are cartilages? So, we all say cartilage tissue, have you seen cartilage? Like, do not think of human cartilage. We can think of animal cartilage which you could have seen?

Student: Yeah.

So, where have you seen animal cartilage?

Student: Chicken.

Chicken, where do you see it?

Student: The bone; it is just on the bones surface.

On the surface of the bone. So, if you have eaten chicken, what you would have seen is the leg piece of the chicken would have glassy material on top. So, that is the cartilage. The one which shown here is knee cartilage. So, this articular cartilage defect can actually be very painful. If you have damaged cartilage, your walking would be a painful process.

Because of this, the quality of life, especially for an elderly patient, is significantly affected. This damage can also happen for athletes during some injuries or if you are in an accident and so on. And age, trauma, all these things can also cause this kind of damages. This is quite common. A lot of people have this and do not confuse this with a ligament tear. Ligament tear is different from a cartilage defect. The ligament is basically just elastic tissue which ties the bones together.

So, the ligament tear is different from a cartilage defect. The cartilage defect is a lot more painful. Cartilage is avascular, aneural tissue, and it does not heal on its own because it has very low cell density, and they are very low mitotic activity. There is also very little cell migration to these tissues.

Because of this, the tissue does not heal on its own. So, you need to provide some kind of supportive environment for it to heal. So, people have tried to do different things. So, we will look at some of the therapies which are currently being employed and how they have been established.

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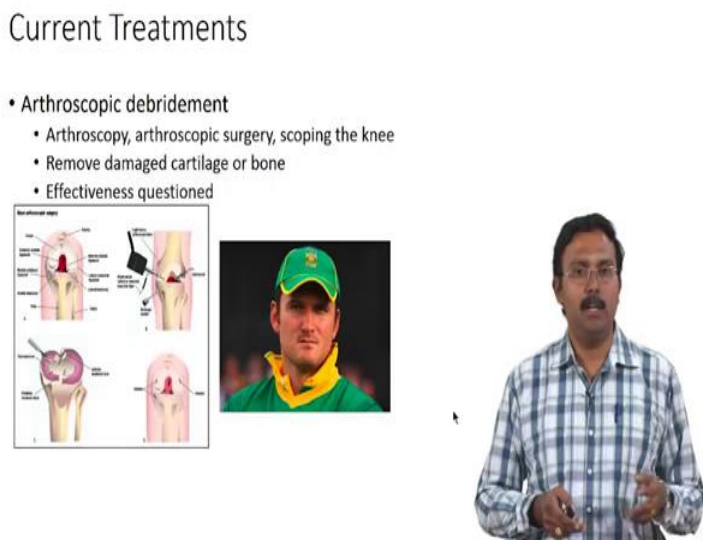

So, one term you would have seen is arthroscopic debridement. It is also called as scoping the knee or arthroscopy. People who follow sports would have seen this quite commonly. So, many athletes go through this. This is basically just a cleanup procedure. When your cartilage damages, what you are going to have is small bits and pieces which are going to be lying around. So, this is going to cause more pain for the person. Scoping

the knee basically just removes the damaged cartilage and cleans up the procedure place, so that it can heal in a better fashion. So, there is no continued injury.

Effectiveness of this kind of a procedure has been questioned with respect to its healing effect itself. However, it will definitely help in reducing the pain and alleviating the suffering of the patient. So, Graeme Smith is one cricketer who got it done I think like 7 years back or so. I am pretty sure a lot of soccer player should have gone through something like this and basketball players, all these people go through scoping the knee quite regularly.

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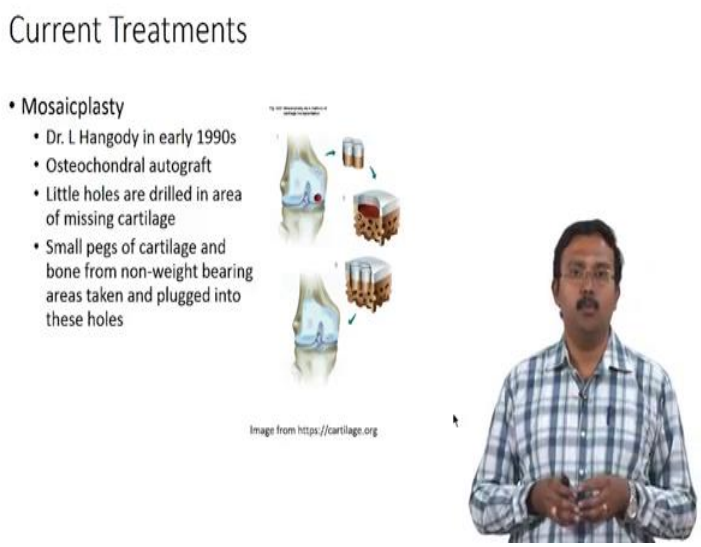

Another procedure is mosaicplasty. So, this is basically an osteochondral autograft. This was developed by Doctor Hangody, and when you have cartilage damage, you take out the debris, you clean this out, and you take pieces of cartilage from a non-load bearing area, and you use that to fill it as pegs.

So, if you can see this image, I do not know if it is very clear here. This is damaged cartilage, and they have actually taken small pegs from here. They have filled the damage here, and you see that with the filled pegs, right.

Are you able to see it? Ok. So, that is how mosaicplasty works. You can Google for more images which actually show surgical images. This is a very simple procedure. However, the problem is you are now damaging another part of the cartilage. Knowing

that cartilage just not regenerate very effectively, you have now anyways created another damage. The only thing is it is in a non-load bearing area compared to the load-bearing area. So, hopefully, the pain will be lesser for the patient.

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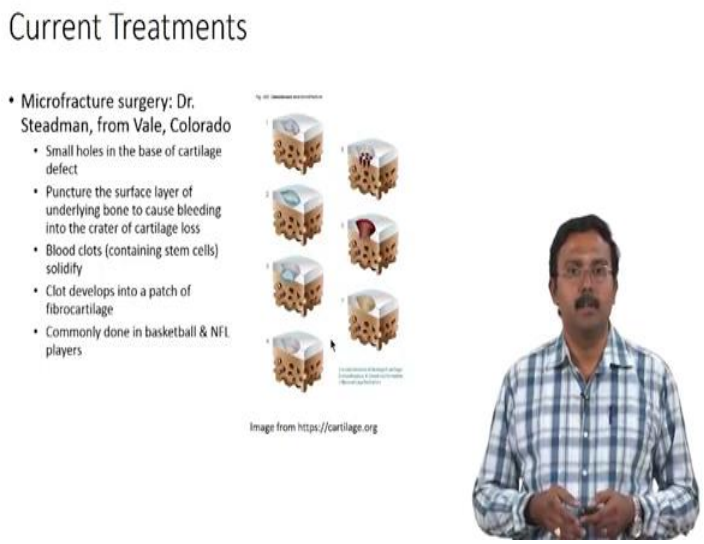

Another type of surgery is microfracture surgery. So, this was developed by Doctor Steadman from Colorado, and here what is done is small holes are made in the base of the cartilage defect. So, again for any cartilage procedure, scoping would be the first thing they do. They will basically clean the cartilage ok.

After cleaning it, they will create small holes, and this punctures the surface layer of the underlying bone, and this will lead to bleeding of the bone, and the blood which comes out will clot, and this will contain stem cells and other growth factors, and this basically forms the tissue, which will then help in regeneration. This is very commonly done for basketball players and like American football players. I do not know soccer players are probably doing this too, not a big soccer fan so, do not know.

This is a very common procedure which is done. This actually is a very serious surgery. The patient can take up to maybe a year for fully recover and get back to their full health ok. They might be able to do regular activities after a few months, but if you are an elite athlete and you want to get back to that level, it can probably take up to a year. So, the problem here is the recovering time is quite long, and also you are causing damage, and

it can be a very painful procedure. You are actually drilling holes on a bone. That is not really going to be an easy thing to survive.

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So, arthroplasty is basically replacing damaged tissue either using partial or total joint replacement and depending on how bad the situation is. So, these are the current treatment, which is done, and I want to look at the tissue engineering-based treatments from here on out.

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So, that is an autologous chondrocyte implant. This procedure was first done in 1987. So, it has been a little more than 30 years, but it is still considered to be experimental by many people. Even after 30 years, we are still exploring this further, trying to optimize it, make it better and so on.

This was popularized by Doctor Lars Petersson. Here you need two surgeries. The first surgery you harvest cartilage from non-weight bearing areas, and then you close the patient up, take the cells, culture the cells in vitro. Once you get enough cells, then you go for the second surgery. Maybe a couple of weeks down the line and you clean the damaged area now, and you place a collagen membrane on the defect and inject the cultured cells.

The cells will now be present; there will help in regeneration. Chondrocytes can actually secrete the matrix they need to culture; they need to grow on. So, the idea is to have these chondrocytes there, and hopefully, they will secrete the matrix, and they will heal the tissue.

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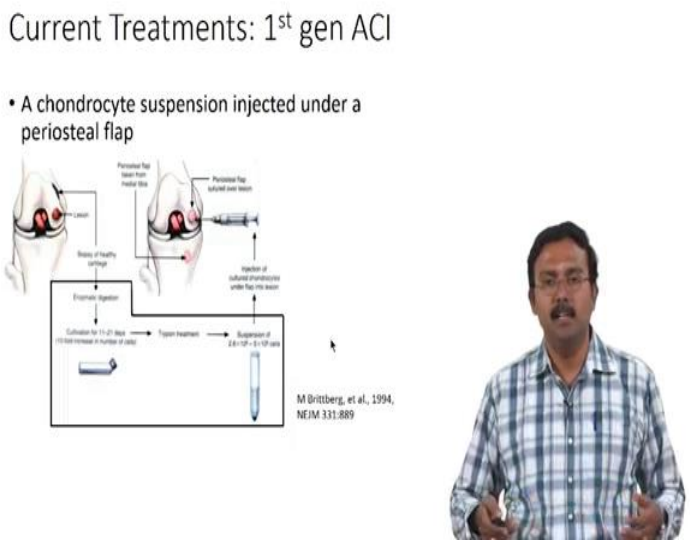

So, there have been three generations of this. The first generation is, which I just explained. So, all you do is take a chondrocytes suspension, and you inject it under periosteal flap. So, this is a small flap which is sutured on top of the damage, and you take out chondrocytes which have actually been cultured, and this is now injected inside

it. The flap is just to make sure the cells do not leak out of place. It will hold the cells there, and hopefully, this will help in regeneration.

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And this was the next generation where a chondrocytes suspension is injected under a collagen membrane instead of using a flap which is again harvested from your own body. Here a collagen membrane was used, and this is actually reasonably effective.

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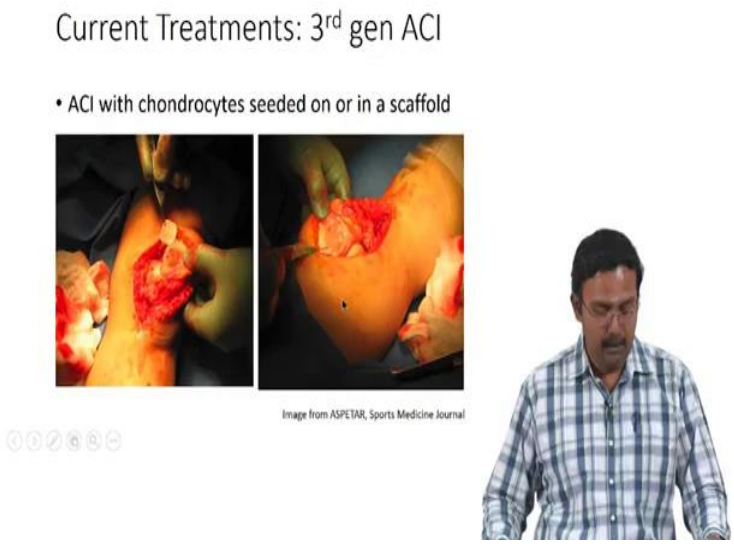

Recently, what people have been doing is, they actually culture the chondrocytes on the scaffold, on a collagen scaffold and then place it in the damaged tissue. So, this also been

quite effective. This is now identified as the third generation of autologous chondrocyte implants.

All this basically gives a summary of what are all the different cell-based techniques and biomaterial-based techniques which are being used. We will discuss a little bit about molecule-based techniques, signaling based techniques which are currently available. So, signaling molecules are usually not used by themselves. Because, these are growth factors or proteins which need to be delivered to the site, so they are usually loaded to some material and delivered.

We looked at what is commercially available and what is currently being done in that domain, and with that, we will come to the conclusion of the basic introduction for tissue engineering ok.

Thank you.