Biomaterials for Bone Tissue Engineering Applications
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Indian Institute of Science Bangalore
Module 08
Lecture 40

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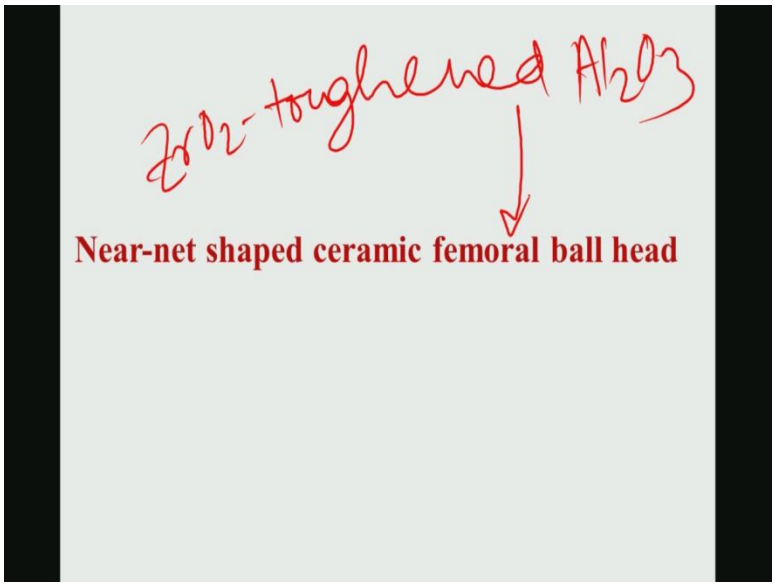

So, in this module I will discuss that the case study of another biomedical prototype development and that is that Zirconate offend Alumina base femoral ball head.

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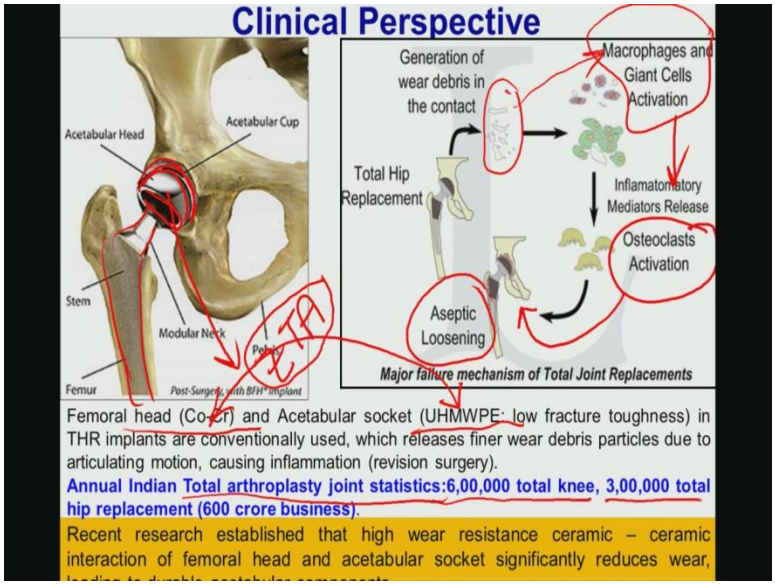

So, this Zirconate offend Alumina based femoral ball heads as I told you in the last module that these particular femoral ball head can be made up of either Cobalt chrome or stainless steel or ceramic and then acetabular liner, acetabular socket this is typically made up of ultra-molded polyethylene. So, this one I am saying that we are planning to manufacture these femoral ball head with Zirconate offend Alumina which is abbreviated as ZTA and ZTA is popularly used in the ceramics community as well.

So, what you see here is that is a typical total hip joint replacement here with this neck of the femur as well as femoral ball head which is fitted here and here acetabular socket and I mentioned in the last module also that femoral ball head typical image of Cobalt chrome acetabular socket highly (())(1.47). Now this kind of combination they do not have the best possible wire resistance property. So, therefore the research worldwide is looking at alternative to the clinic currently clinically used femoral ball head material and one of the potential material or potential class of material is bio ceramics. Bio ceramics means those ceramic materials which can be used for biological or biomedical applications.

Now, one of the material on of the classic ceramic material than people use not only for biomedical applications but also for a large array of fundamental studies that alumina. So, alumina is a very classic ceramic material and it is well tested for different type of properties and so on. So, having said that we have one kind of focus around try to see that how alumina can be adopted in this kind of environment. But the problem with alumina is that despite various other properties which are typical of any ceramic material alumina is not the best best of the toughest ceramic material. Because toughness is the major issue of the ceramics and then alumina is a very poor fracture toughness like three. Whereas Zirconia is one of the candidates ceramic material with large toughness, large means amount the ceramic materials but large certainly not as compact to metallic material. Zirconia can have fracture toughness of 10 mpa square root meter which is kind of relatively respectable number in the ceramics community.

Now, in order to mix that in order to kind of toughen that alumina with little bit of Zirconia, You can produce the Zircona toughened alumina material and in the total hip replacement for in this particles are really is as can be seen here, now these are the major culprits because these particles can do all the different biological or this can lot of significant or biologically significant actions in terms of macro physicians joints and activations.

And that will lead to inflammatory mediatory release and osteoclasts activation. Osteoclast activation means at any point of time in any bone healthy bone if you have more osteoclasts than less osteoblast then bone resumption will take place. And ultimately that leads to aseptic loosening. This is the major failure mechanisms currently understood for the total hip joint replacements and as a result the divisions actually is only alternative as per the clinical action is considered.

Just to give you that how good how badly that clinical fraternity they need this femoral ball head development, in India itself according to the total arthroplasty joint statistics that six lakhs of total knee and three lakhs of the total hip replacement is there is is currently conducted and we have also discussed in the one of the earlier modules that we have developed this some of the new material for a acetabular socket HDPE HA alumina.

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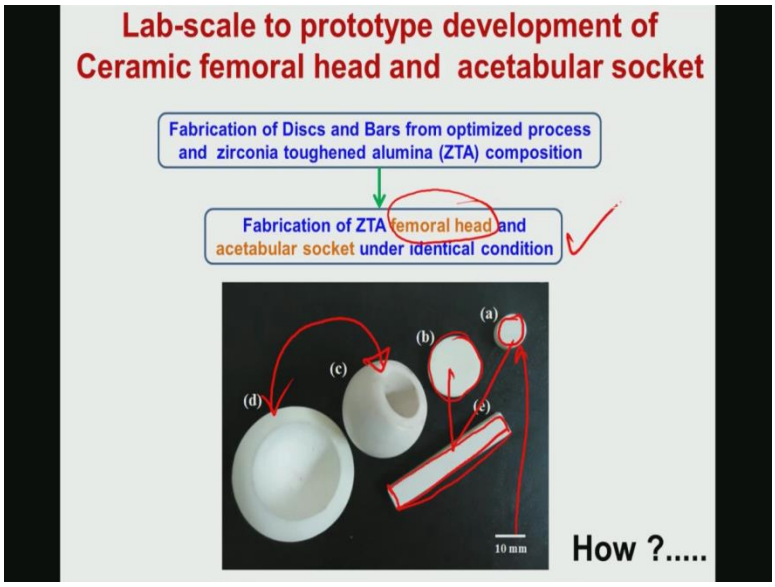

So, this is essentially existing ultra-molecular polythene socket and so, what we have done, we have done essentially the lab scale research just to produce different simple shaped materials. So, this is your kind of 10 mili meter diameter, cylindrical shaped then you can do this 20 or 30 mili meter cylindrical sample as well as some rectangular bar of 40 to 50 mili meter. Now all these materials of simple shaped were developed to measure a number of material properties like hardness, fracture toughness, wire resistance or initial cell compatibility study and so on.

But the real challenge is to make this kind of geometrically complicated shapes which is not very easy and often you cannot use the lab scale processing conditions or lab scale sintering conditions you cannot adopt the same lab scale sintering conditions to fabricate this kind of acetabular socket or femoral head. So, one has to tune or tailor, the lab scale conditions to produce this kind of geometric shape. Now this fabrication of ZTA femoral head and acetabular socket that I will show you at least a femoral head.

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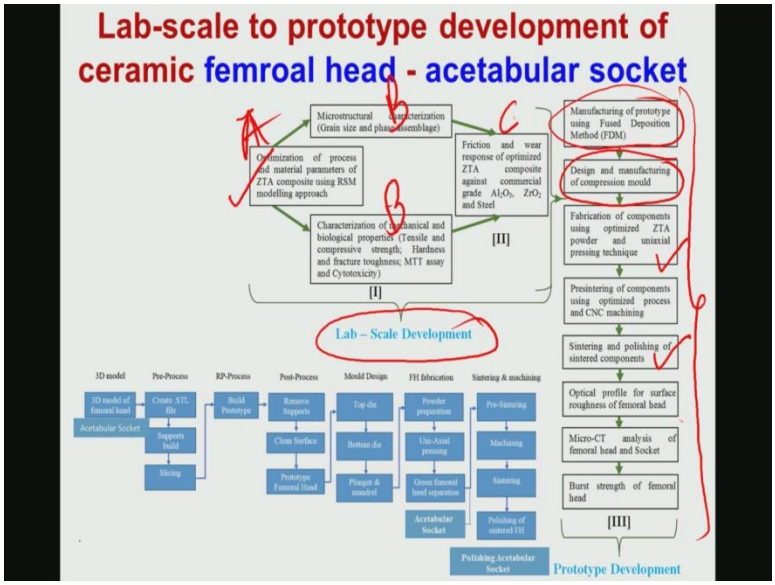

Now, like before or like in earlier module that lab scale development requires that optimization of the sintering conditions that is that is A and then microstructure characterization and mechanical property like is par elements of the material size then C is your fiction and wire properties like the way I have shown you in the last module like in the context of the development of ISDP hap of alumina composite. And this is the kind of prototype development then it starts with that again fused position method FDM, I add design and manufacturing and compression mold, then ZTA uniaxial pressing condition, those things I will explain to you slowly. And sintering and polishing conditions polishing of the components, optical profile and micro competent tomography analysis of femoral head and socket.

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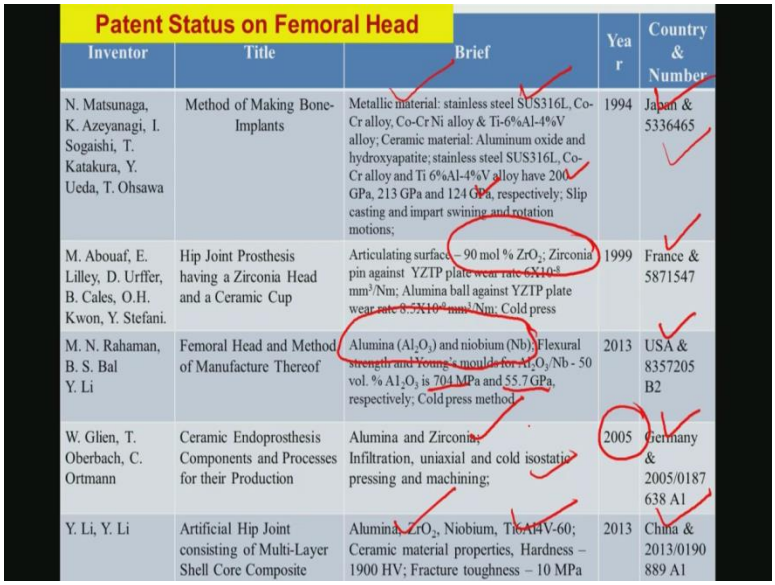

Patent Status on Femoral Head

Inventor	Title	Brief	Year	Country & Number
N. Matsunaga, K. Azeyanagi, I. Sogaishi, T. Katakura, Y. Ueda, T. Ohsawa	Method of Making Bone-Implants	Metallic material: stainless steel SUS316L, Co-Cr alloy, Co-Cr Ni alloy & Ti-6%Al-4%V alloy; Ceramic material: Aluminum oxide and hydroxyapatite; stainless steel SUS316L, Co-Cr alloy and Ti 6%Al-4%V alloy have 200 GPa, 213 GPa and 124 GPa, respectively; Slip casting and impart swining and rotation motions;	1994	Japan & 5336465
M. Abouaf, E. Lilley, D. Urffer, B. Cales, O.H. Kwon, Y. Stefani.	Hip Joint Prosthesis having a Zirconia Head and a Ceramic Cup	Articulating surface – 90 mol % ZrO_2; Zirconia pin against YZTP plate wear rate $6X10^{-8}$ mm^3/Nm; Alumina ball against YZTP plate wear rate $8.5X10^{-8}$ mm^3/Nm; Cold press	1999	France & 5871547
M. N. Rahaman, B. S. Bal Y. Li	Femoral Head and Method of Manufacture Thereof	Alumina (Al_2O_3) and niobium (Nb); Flexural strength and Young's moulds for Al_2O_3/Nb - 50 vol. % Al_2O_3 is 704 MPa and 55.7 GPa, respectively; Cold press method	2013	USA & 8357205 B2
W. Glien, T. Oberbach, C. Ortmann	Ceramic Endoprosthesis Components and Processes for their Production	Alumina and Zirconia; Infiltration, uniaxial and cold isostatic pressing and machining;	2005	Germany & 2005/0187638 A1
Y. Li, Y. Li	Artificial Hip Joint consisting of Multi-Layer Shell Core Composite	Alumina, ZrO_2, Niobium, Ti6AlV-60; Ceramic material properties, Hardness – 1900 HV; Fracture toughness – 10 MPa	2013	China & 2013/0190889 A1

Now so, some of this earlier results or earlier reports this, this reports many of them are not available in that open literature. Because these are like some of the patent disclosure, invention disclosure and this patents are filed in different countries around the world like Japan, France even say Germany and China. So, as you see that 5 different countries we have taken, 5 different patents just to illustrate you that what is the current status of this femoral head development.

Now, to remind you that that these materials that they are patented they are not mostly they are the kind of either metallic material like stainless steel or cobalt chrome alloy and so on which has sudden hardness value, elastic modulus values and strength values or people have done some of the 90% Zirconia and some one group in the USA they have developed Niobium doped or Niobium added alumina, Niobium reinforced alumina and they have reported the strength and in elastic modulus in some around 704 mpa and 55.7 mpa. One group in Germanyhas patented in 2013 that is Aluminium Zirconia that is uniaxial code isostatic pressing and machining. And then another one is that in China that is that Alumina Zircona and Niobium and Didymium6 Aluminium, 4 Vanadium based materials.

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As I said that first eight for the prototype development is the engineering design. So, therefore I am showing you that what is that CAD file, CAD design file of this material design. And you can see that various dimensions that are mentioned and then ultimately your aim is to translate that design concept into the prototype product by certain intrigued manufacturing protocol.

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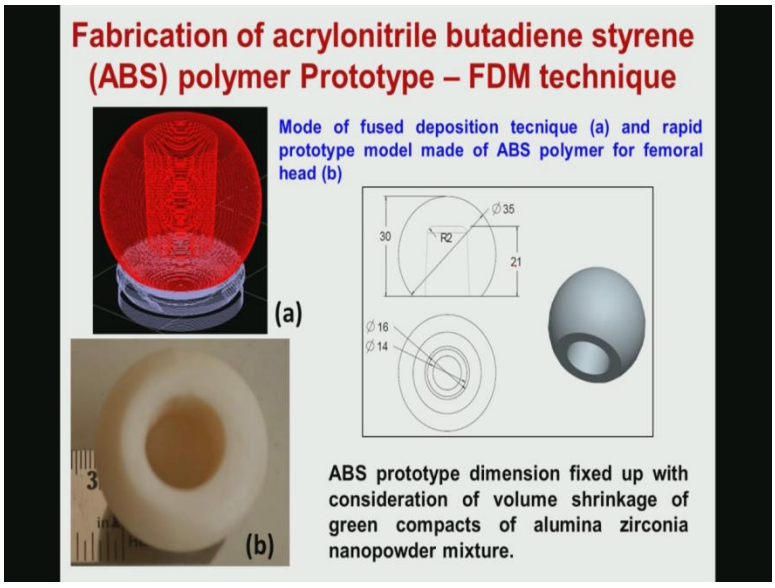

So, here again you have to first develop the mold where this ceramics is to be fabricated. And this mold essentially is made by that FDM technique which is the rapid proto typing technique.

You can use that ABS as the polymer that is the very standard polymer for you which is used in the this prototype fabrication process.

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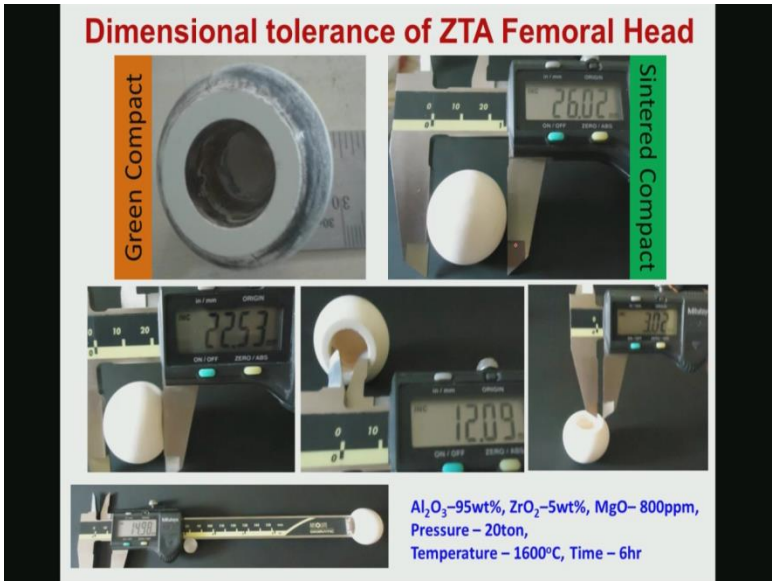

Now after that you can do this prototype fabrication then you do the green mo… green compact and then you make this equivalent of hindalium as a green compact and then you can do pre sintering. Green compact means is a large uniaxial compaction pressure you can you apply to this material femoral head and then you can make the green compact. After that you can make the pre sintering and pre sintering can be done at 1200 degree Celsius and so on. And if if in the pre sinter stage if here is certain dimensional if the sample goes little bit of high from that original dimension then you can do very mild machining also. Because pre sintered it is not a fully sintered but it is good enough that you can do little bit of the machining not that much. So, tailoring on the intermediate machining process is very important. And then after that you can do sintering the final sintering and after that final sintering then you can do this what is that typical wall thickness of this material femoral head.

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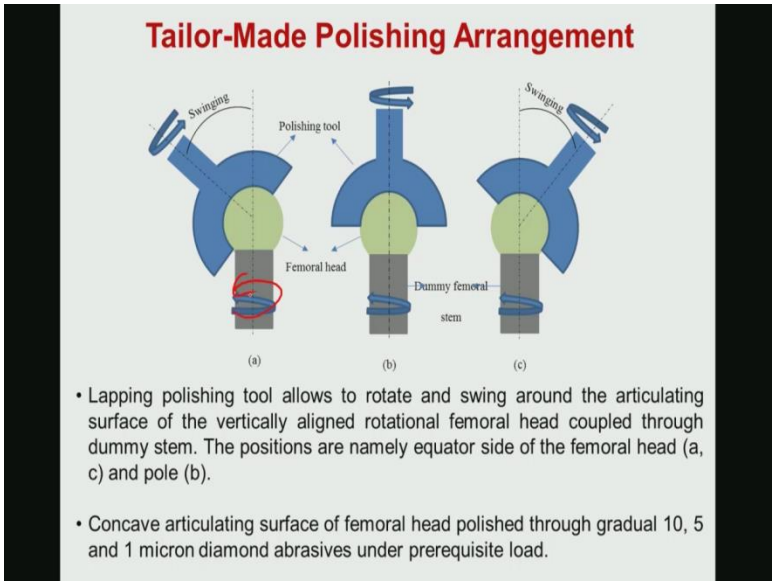

Now, one of the important things this inter manufacturing process is how you make the polishing of the final surface or the upper surface of this machine. This polishing is not a very simple polishing because it is not like a flat sample polishing. But it is a rather carved sample polishing. So, therefore you have to use certain swinging type polishing machine, polishing tool which will alternate its position during the polishing even itself and it can come in a reciprocative emotion and this entire sample, entire femoral ball head also needs to be rotated during this swinging that polishing tool itself. So, with this kind of with this kind of technique you can get that outer surface of the femoral ball head in the right polished condition.

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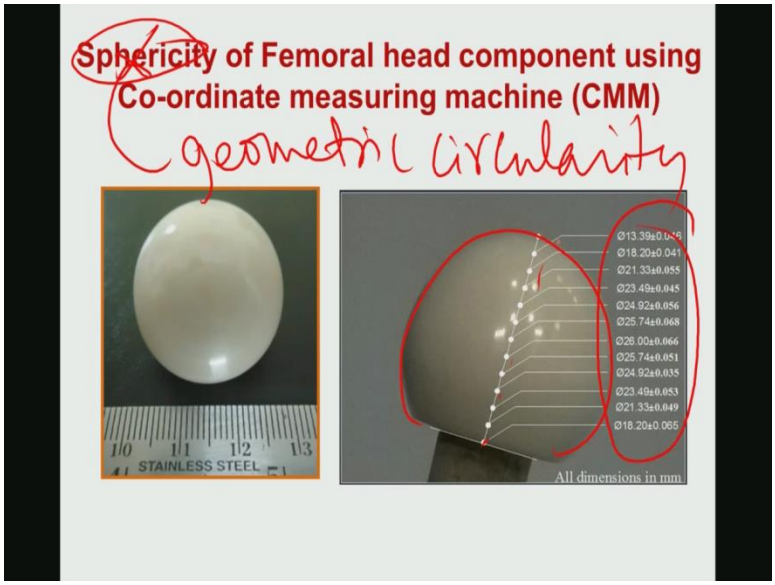

Now, this one has to measure the sphericity of this material so, geometric circularity that instead of sphericity that we also call is a geometric circularity. Now in this geometric circularity you can find out that what is the different dimensions of these materials and how this materials is polished and smoothly polished materials. And different points you can measure this and see that what is the design file and what is the product file what is the product file.

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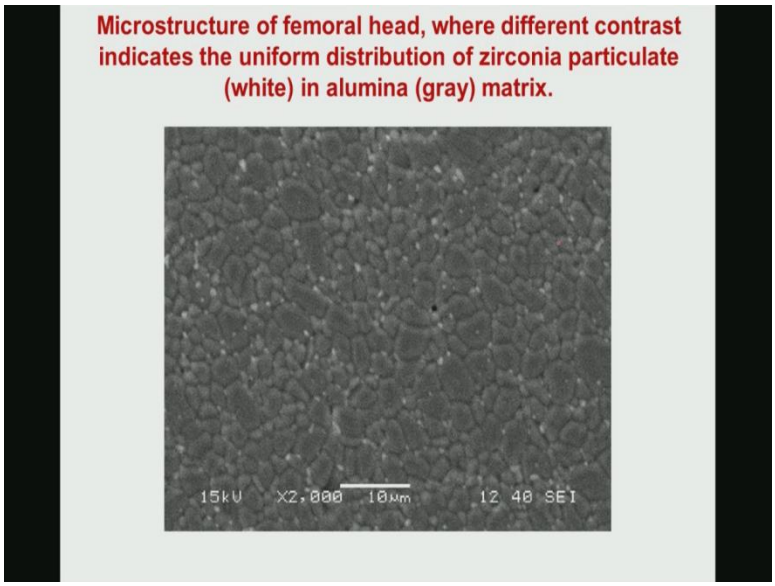

Now, microstructure one has to see that you take a one sections of this femoral ball head and this is the scanning electron microscope image of the thermally etched samples. Thermally etched means you take the sample you polish it you heat it at a temperature which is 200 degree or 100 degree lower than the original sintering temperature. For a very few for for a very brief time like 50 minutes to 30 minutes and then this thermal etching process typically can reveal the microstructural grain size or grain size distribution in the polished cross section.

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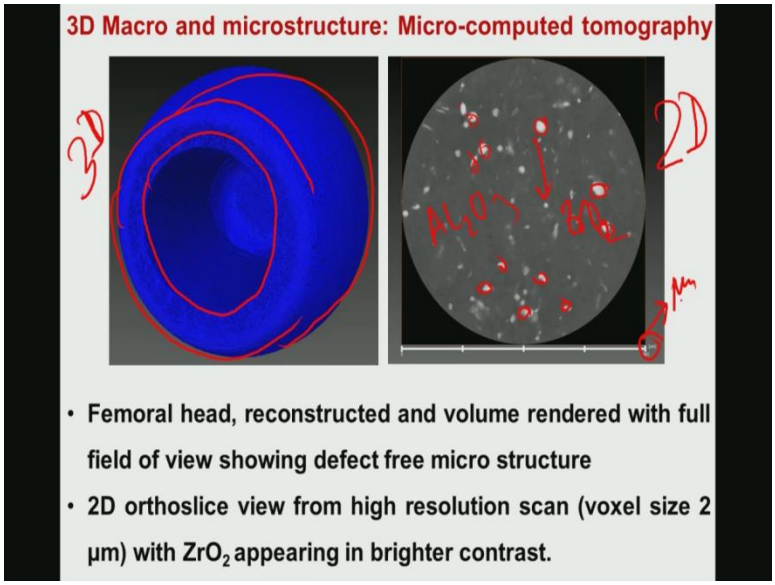

So, once you polish it once you see the microstructure once you measure the properties and so on. One of the one of the one of the important feature in this kind of prototype development is to quantitatively and qualitatively determine 3 dimensional macron microstructure. And the technique that we use is that micro computed tomography. Now what do you see in the left hand slide it is the 3D volume rendered image of the femoral ball head. Now 3D volume rendered image will allow you to see that how this material follows this shape and size with respect to the design file.

The right hand side image is called 2D orthoslices. 2D orthoslices will tell you this different contrast particles with different contrast so, this is most the Zirconia particles and rest is your alumina matrix. So, this Zirconia particles what is the size? Because you know that what is the micrometer here micrometer. Now with the use of the several of this 2D orthoslices section and

3D cycle, you can essentially quantify that what is the Zirconia particle size A and B, how this Zirconia particles size is distributed in the femoral ball head structure.

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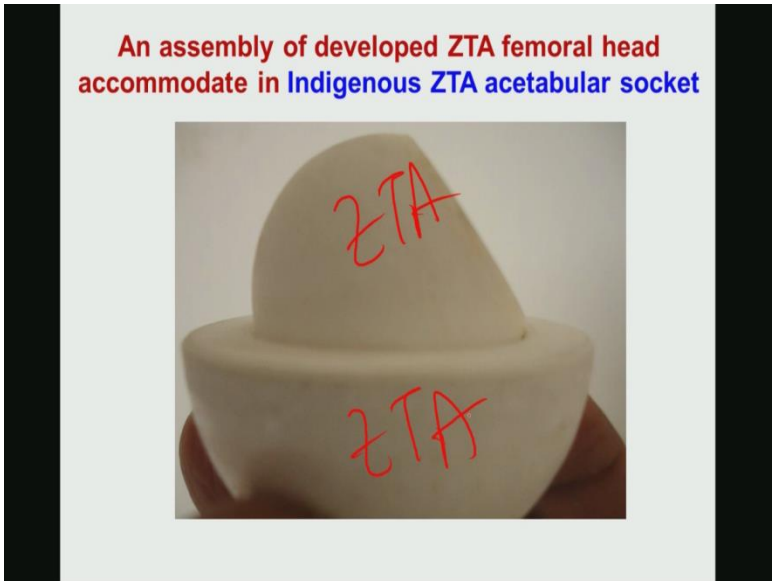

Now this this is one of the assembly of the femoral ball head, this is the ZTA femoral ball head and this is the ZTA femoral socket. Now in the as fabricated without any machining in the Neoschip fabrication conditions you can see that what is the geometric conformity of this ZTA femoral head with acetabular socket. Essentially it shows that it is essentially a good conformity.

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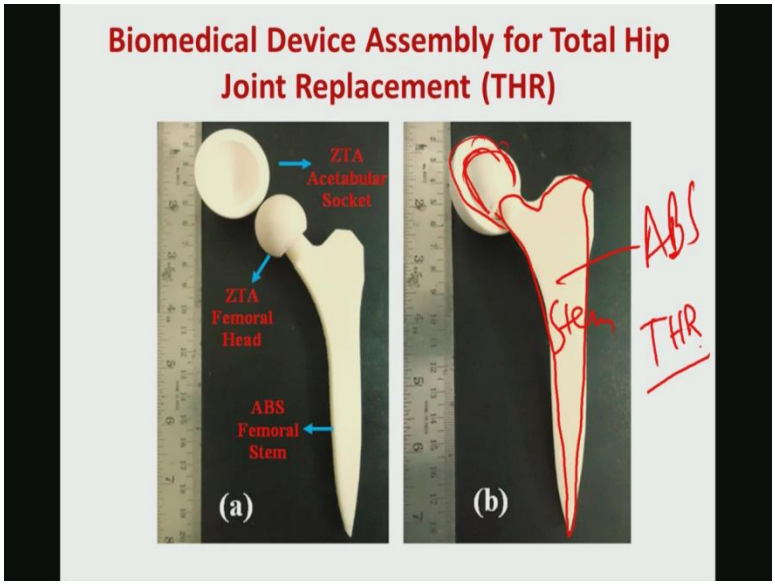

Now just to show that how this entire assembly will look like you can essentially make this femoral stem with the help of that ABS prototype polymer now AB ABS polymer then you can make this stem prototype, then you can put this strain prototype the neck into the femoral head here and then femoral head you can see that what is the geometric conformity with respect to the acetabular socket. So, this entire THR assembly if you see that with respect to the design files, how it is getting fitted into that actual scenario.

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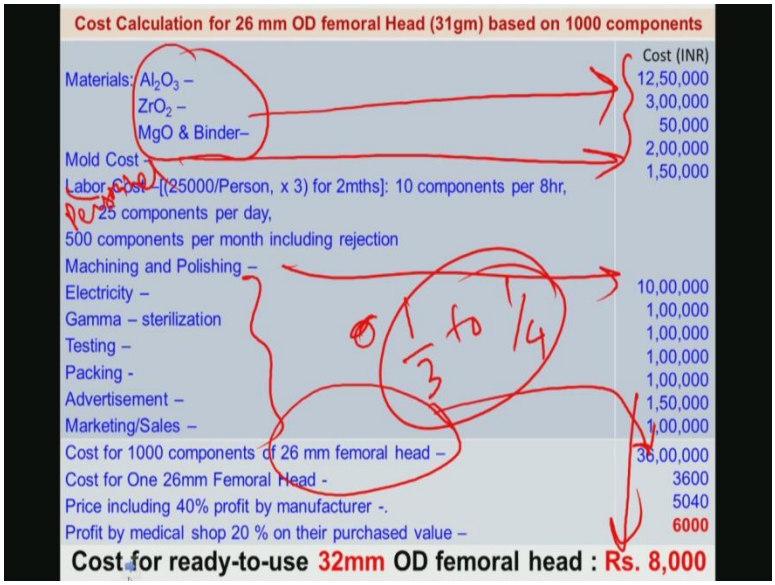

Now, this kind of device fabrication technique one of the things that one has to really understand that what is the typical size, what is the typical cost estimate of this femoral femoral ball head. And then and then there you can see there you can see that what are the typical powders that you use, what is the cost of these powders. So, this is the Indian scenario I am talking. Then, when you make this mold, what is the cost of the mold, what is the typical labour and what is the personal cost, labour cost or personal cost and what is the machining cost and polishing cost, electricity and other other things. We have done the rough estimate and we are finding the 26 milimeter femoral head cost you around 6 to 8 thousand rupees and 32 milimeter cost you 8 thousand rupees.

Now if you compare with any of these commercial available materials this femoral ball head cost this particular process at least 1 third to one forth of the cost. Now, this is again I say very rough estimate, but certainly it shows that the approach processing approach or integrated

manufacturing protocol that we have adopted that will be that will be scalable and that will be commercially viable and that is kind of a cost effective technique in the present scenario.

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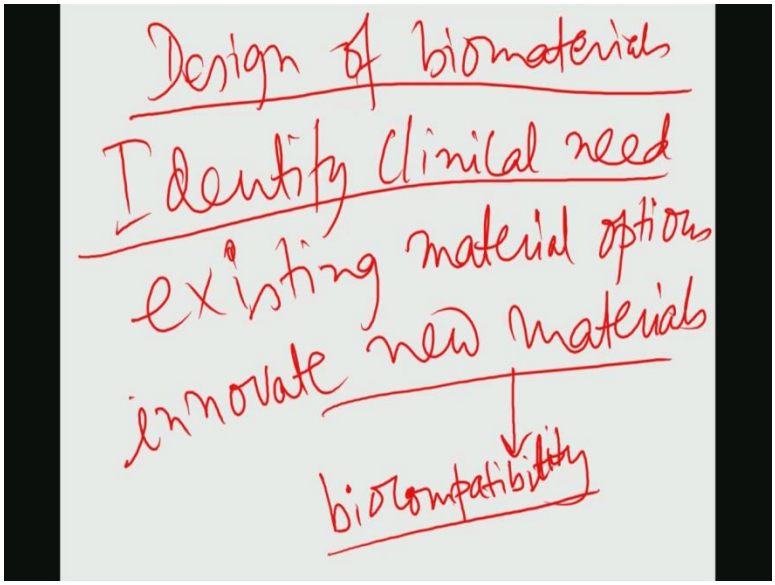

Now, this brings us to the end of this this particular module, but before I close that one of the things that I need to mention to you is that I need to summerise these inter course quickly and I need to do this I want to do this without any slides but just to give you my own perspective.

So, the first thing in any biomaterials development you have to design, you have to design that biomaterials and design the biomaterials essentially means you have to first identify clinical need. Now in the context of the genuine applications or orthopedic applications first one has to interface with the orthopedic surgeon or the dentist or (())(18:17) and so on. Then you identify the what is the clinical need then you understand that what is the clinical need then you see that what is the existing material option.

Now once you that what is the existing material options you have to also know that what are the problems with the existing material option. Once you know that what is the existing problems with the (mate) currently clinically currently clinically used materials, then you have to innovate how new materials can be how how to innovate new materials that you can conduct research in the laboratory and further take it further.

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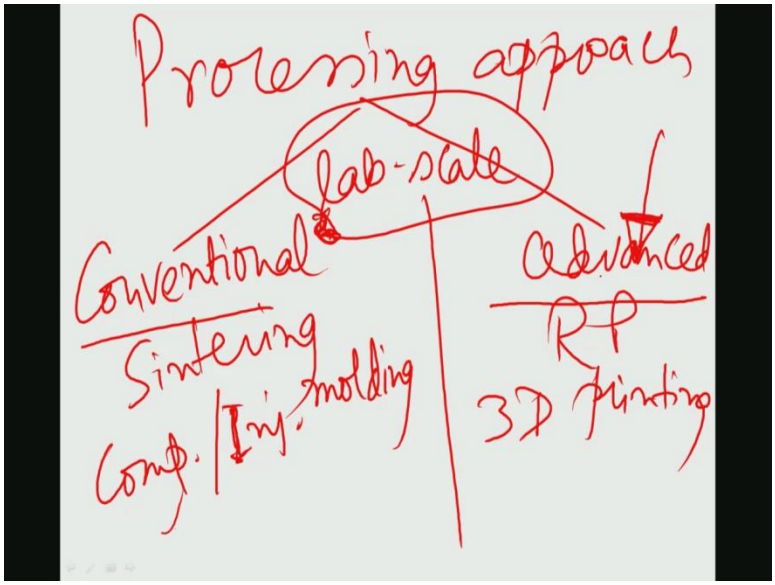

Now, in this materials new materials as for the choice of materials is concerned you have to see the literature and see that whether biocompatibility property of these materials are already established or not. Ok? Now, in this particular context you have to also understand that mechanical property should not be given primary primary considerations should not be given should not be given over overwhelming importance in the selection of new materials because it is biological applications, so, biocompatibility property should be given primary importance first. Now once you do that next thing you have to see that what is the processing approach that one has to adopt?

Now, this processing approach is different for different kind of classes of materials that metals it is different, ceramics is different, polymers it is different. Now processing approach you can use like conventional processing approach or you can use more advanced processing approach. Now advanced processing approach you are coming, you can do that rapid prototyping like 3D printing, 3D plotting and so on. Or conventional processing approach can be either sintering or compression or injection molding in case of polymer. Now all those things essentially give you, all those things typically is used in the lab scale development of the materials.

So, lab scale development essentially means that is a very simple shaped shaped simple shaped materials that you can you that you can develop without even considering that either these approach can be ultimately adopted to develop that complicated shaped biomedical device. The

way I shown couple of examples like one is femoral head and one is acetabular socket. What is the other considerations here in the conventional approach? Most often you cannot take the patient's specific design except like compression molding mold or something. In the advance processing approach like rapid prototyping you can make or you can fabric at the patient's specific implants. That means you can take the CT scan data from the patient and you can convert it into the rapid prototyping or we can translate the design to the product using any of the rapid prototyping technique. So, this is the two advantages.

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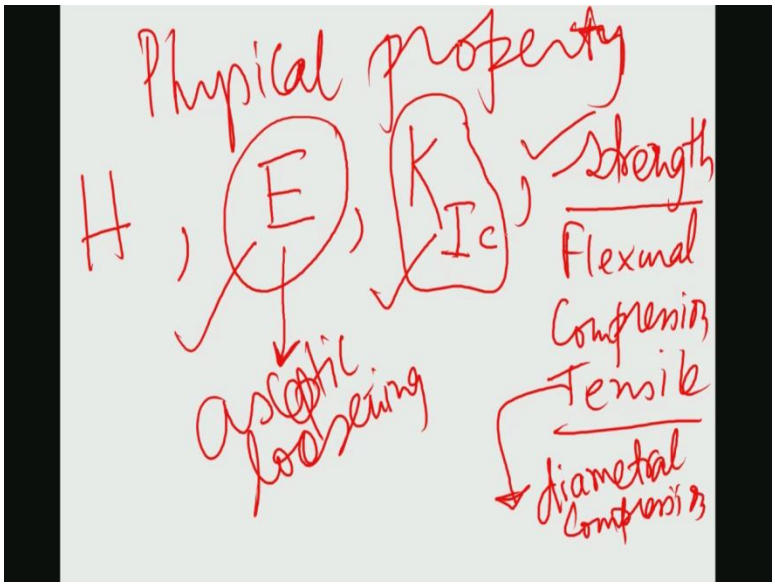

Now, third thing is that physical property characterization. Now physical property characterization means like in in biomaterial literature often people say physical property in a material science literature, people say mechanical property. Now physical property means you can use the hardness, you can use elastic modulus, you can use fracture toughness that is critical stress intensity factor under mode 1 loading. And you can use where several strength parameters. Now elastic modulus by far is the most important as per the orthopedic application is concerned.

Because elastic modulus the mismatching elastic modulus to a large extent can cause aseptic loosening. Ok? And therefore as we elastic modulus is one of the important factor, strength factor means strength is important because it is the major of the load bearing capability of any implant. Now strength can be of different this one, one is that flexural, one is that compression strength. In the polymer one can measure that tensile strength or in metals also you can make

tensile strength in ceramics. You cannot measure the inside strength in a conventional manner that you do in ceramics or metals or polymers. But instead what I have shown in one of the cases you can do diametral compression testing ok?

So, I am trying to re capitulate all the things I have taught you in several of the modules past modules. So, diametral compression strength, now once you measure this kind of properties in the ceramics special attention should be given to fracture toughness. Because fracture toughness is physically tells you what is the resistance towards the crack growth by given micro structure. So, larger the fracture toughness essentially means larger would be the resistance against the crack propagation.

So, if the material A,B,C,D is there you are developing and out of that you see that which of this material among this material A.B.C.D has that best possible combination of the bone mimicking properties in terms of elastic modulus, in terms of fracture toughness, in terms of strength. So, one material can have a very close elastic modulus of the natural bone but that may not be that may not have the best possible combination of fracture toughness and strength. So, you have to have some balance between all these properties, you select that particular material then you do all the detail In-vitro, Cytocompatibility testing.

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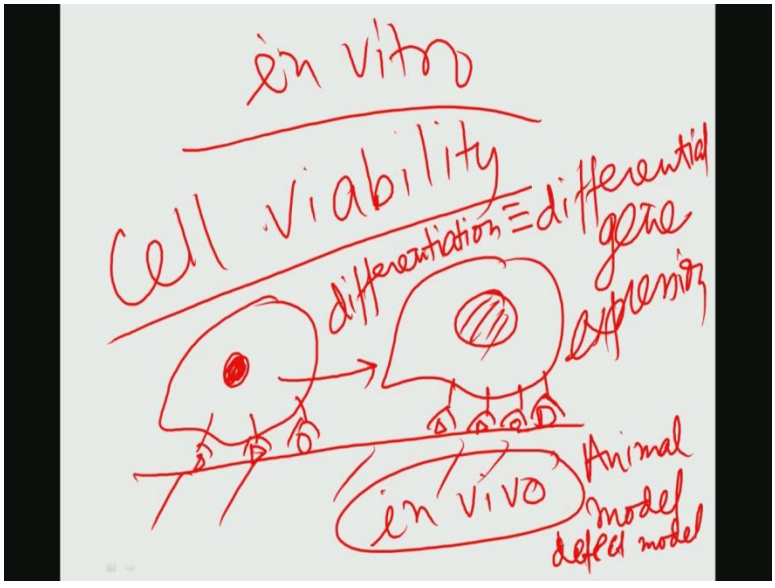

Now, In-vitro cytocompatibility testing that typical material cells people they are often satisfied with the cell viability results. But if the field if the biomaterial science or if the biomaterial science or biomedical engineering the way it is today it has developed quite far but 10 years ago simple cell viability result would be sufficient to publish a good paper in one of the highly paid channel. But in today's world our understanding has developed and it is matured to extent, then one would like to see that when a biomaterial substrate when a cell is adhering, first of all you see that what is the morphological changes of the cell and if you remember this protein adsorption and all those things that I have shown you that whether a there is any visible change in the cell functionality or whether there is any quantifiable measure of the cell functionality when this material when the cell is adhering and growing on the material.

So, as I said that any time the cell undergoes differentiation, this is not the differentiation in a mathematical context, but this is the differentiation means differential gene expression. So, when the differential gene expression has been there and it is to be quantified, so, differentiation essentially means that is the differential gene expression. So, whether there is any the change in the functionality, so if you develop some materials which has a best possible physical properties at the same time it can not only be used as a cell growth substract like on which cells can comfortably grow over different time point in culture, but at the same time the cell substract can be used as the for the differentiation of left stem cells towards the bone cells. That is the ideal for the orthopedic applications or bone replacement applications. And those kind of substracts or those kind of materials are much more attractive compared to the conventional materials which can only support the cell growth. I hope I made this point rather clearly.

Now once you once you down the cell In-vitro, the next thing is that you have to see that the next thing is that In-vivo. So, the pre-clinical study is very important and here I have emphasized some of the lectures that animal model and defect model. Now for the bone replacement applications, the defect model is often people use is that, femoral defect model like cylindrical defects you drill the cylindrical hole in the femur and then you implant your material and then see that what is the bone regional cell over different time point. In another model is that what I have in some of the modules is called segmental defect model or critical size defect model. So, all these defect models often provide complimentary information on the bone regeneration capability around the material in a particular experimental animal.

So, other thing that I have emphasized in one of the earlier module and then I must repeat here that In-vivo study for any of a new material that you have developed in your lab must go through a series of a series of animal study. You have to first start with the let's say for bone it is the rabbit animal experiments. One of the rabbit animal experiments provide you satisfactory or or useful results or that or establishes that tissue compatibility of the materials. Then that small animal model experiments need to be validated at the larger animal model. So, first is rabbit then you have to go to goat model or sheep model ok?

Now once you validate your lower animal lower animal test results in that intermediated relatively large animal test results, then only you can go for the clinical trials on human patient subjects. Now this clinical trials is ethically quite challenging one has to take the approval not only from institutional ethical committee but also in the national regulatory committee. Once you do all those clinical trials then only that material can be can finally see the light of the day and you you can transfer the technological biomedical company and you can take that before that you can take the national regulatory committee approval like the United States or similar regulatory approval in other countries and then a company can produce the materials in multiple numbers and sell it to the hospitals and so on.

So, I think with this with this course I have covered a broad spectrum of knowledge with you, so that you are in a position to to design your experiments to understand and analyse your results in the light of the biocompatibility evaluation as well as design new materials and lastly new implants and devices so that, this research becomes a very useful to the society as well as the larger cross section of the patients.