Uses of metals and materials in some specific fields of medical science with an emphasis on problems and prospects

A thesis submitted in partial fulfilment of the requirements for the award of degree of

Master of Technology in Material Engineering

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By

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Declaration Of Originality And Compliance Of Academic Ethics

I hereby declare that this thesis "**Uses of metals and materials in some specific medical fields with an emphasis on problems and prospects**" contains literature survey and original research work by the undersigned candidate, as a part of his Master of Technology in Material Engineering . All information in this document has been obtained and presented in accordance with academic rules and ethical conduct.

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Certificate

This is to certify that the thesis entitled **"Uses of metals and materials in some specific fields of medical science with an emphasis on problems and prospects"** has been carried out by **Mr. Tushar Das (Examination Roll: M4MAT22008 and Registration No. 154370 of 2020-2021)** under my guidance and supervision and accepted in partial fulfillment for the degree of Master of Technology in Material Engineering from Jadavpur University. To the best of our knowledge the contents of this thesis or any part thereof have not been previously submitted for the award of any degree or diploma.

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The foregoing thesis is hereby approved as a creditable study of an engineering subject and presented in a manner satisfactory to warrant acceptance as pre-requisite to the degree for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn there in but approve the thesis only for which it is submitted.

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Abstract

Metals and materials (ceramic, polymer, composite etc.) have tremendous scope in medical science. so many researches are going on in these materials to improve its characteristics and applications in human body and many data, theories are available discretely. Perhaps there is no comprehensive study of applications and importance of these metal and materials available. so, the purpose of doing this project is to make a comprehensive study of importance of these metal and materials in medical science. So, application of materials is used in recent time and advancement in each and every field of medical science is studied and what are the advantages and disadvantages of these materials after applications in human body are reviewed. Then a theoretical attempt to give idea about modification of material after consulting the practitioner of specific medical fields is given to overcome these limitations by technological advancement and upgradation the materials for the benefits of society and medical science.

Chapter 1: Introduction

1.1 Introduction to Material science

Material science includes the idea of physics, chemistry and engineering. Materials have significant impact in our life. Materials are used to create all engineered product. Material science has a long and illustrious history. Historically, the development and progress of societies were closely linked to the ability of the people to produce and process materials to meet their needs. In fact, early civilizations were identified by the level of their materials development (Stone Age, Bronze Age, Iron Age) [1]. Only a few numbers of materials were available to the earliest human, those that occur naturally: stone, wood, clay, skins etc. They eventually developed procedure to create materials that had better properties than those of the natural materials; The field of material science covers the design and discovery of new materials. Materials science became more widely acknowledged as a distinct subject of science and engineering in the 1940s. Transportation, housing, clothes, communication, recreation, and food production-virtually every aspect of our daily life is connected by materials to some degree or another [2].

Materials science is the study of how processing affects material structure and, as a result, material qualities and performance. A better understanding of processing structure-properties correlations has helped nanotechnology, biomaterials, and metallurgy. The creation of variety of technology has been integrally related to the availability of appropriate materials that makes our life so convenient. A breakthrough in the understanding of a material type is often the catalyst for a technology's advancement. We now rely on our capacity to modify basic components to create even more advanced materials (metal, polymer, composite materials, ceramics, electronic materials, biomaterials, and so on) [3]. Since material science is the study of structure and processing of the materials, the knowledge of this science can impact the industry greatly. In the engineering field, for designing any components, we have to choose first the suitable materials from the thousands of other materials with required properties, sometimes it is very difficult to match the design criteria with the existing property of the material, other thing that we should consider whether there is any deterioration in the material with time and cost of the finished product. Sometimes it has been seen that the required properties of the materials are met with the design criteria but the materials are very expensive. so, the more knowledge of material science like characteristics and structure properties of materials helps us to process the required material according to our necessity.

Material science provides numerous societal benefits since it is a science that is constantly looking for methods to improve existing materials and components; it is forward-thinking, which leads to a consistent stream of innovation that benefits the engineering sector [4].

1.2 Introduction to medical science:

The field of science that studies disease diagnosis, treatment, and prevention is known as medical science. Medical science covers a variety of subjects aimed at explaining how the human body works. Starting with basic biology, it is divided into specialisations like as anatomy, physiology, and pathology, with some biochemistry, microbiology, molecular biology, and genetics etc. One of the most significant achievements in expanding life expectancy is medical science. Medical science encompasses everything from medicine to medical diagnostics to medical equipment. This provided us with a greater grasp of anatomy, physiological function, cells, and DNA, among other things. Medical science is currently one of the most important sciences in terms of utility [5].

While practically all other disciplines of science are working to improve human life, medical science is concentrating on giving humans more and more life. People get sick and injured. These issues lead to morbidity and mortality. Medical science allows development of evidence-based treatments and understanding of disease that can be used to reduce morbidity and mortality. For some strange reason, people seem to value things that help them live longer and healthier. Therefore, medical science is important. It gives for a better grasp of what goes into basic research discoveries and medication development from a clinical standpoint. This study has a significant role to play in medical research, and when combined with basic science, it has the potential to improve medical knowledge, discovery, and treatment [6].

1.2.1 *Branches of Medical Science*

The main branches of this science are:

1) ***Basic sciences of medicine****:* This is what every physician is educated in, and some return to in biomedical research. It includes anatomy, biochemistry, histology, biochemistry, endocrinology, immunology, microbiology, neuroscience etc.

Anatomy is the study of an organism's physical structure. Cytology and histology, when compared with macroscopic or gross anatomy, are connected with microscopic structures. The study of the chemistry that occurs in living creatures, particularly the structure and function of their chemical components, is known as biochemistry. Light microscopy, electron microscopy, and immunohistochemistry are used to analyse the architecture of biological tissues. Immunology is the study of the immune system, which in humans comprises both the innate and adaptive

immune systems. The study of microorganisms such as protozoa, bacteria, fungus, and viruses are known as microbiology. The term "neuroscience" refers to a group of scientific disciplines concerned with the study of the nervous system.

2) ***Medical Specialities:*** There are many subspecialities (or subdisciplines) of internal medicine.

Cardiology is the branch of medicine concerned with the heart and its disorders. Dentistry is the study of people's teeth and how to treat dental and mouth issues. Endocrinology is the branch of science and medicine that deals with hormones. hormones and endocrine glands. Gastroenterology is a branch of medicine that focuses on digestive problems. Geriatrics is the study, treatment, and care of elderly individuals and their illnesses in medicine. Nephrology is a branch of medicine that deals with kidney problems. The study of the nervous system and the disorders that impact it is known as neurology. The branch of medicine that deals with bone injuries and treatment is known as orthopaedics. Pulmonology, sometimes known as pneumology, respirology, or chest medicine, is a branch of medicine that deals with the lungs. Ophthalmology is a branch of medicine that deals with the diagnosis, treatment, and prevention of eye and visual system diseases. The study of the anatomy and diseases of the ear is known as otology.

Other inter-discipline branches include:

Biomedical engineering is a branch of engineering that focuses on applying engineering ideas to medical practise.

Forensic medicine deals with medical issues that arise in legal situations, such as determining the time and cause of death, the type of weapon used to inflict injuries, and reconstructing facial characteristics using the deceased's bones (skull) to aid identification.

The study, diagnosis, and medical treatment of problems of the foot, ankle, lower limb, hip, and lower back is known as podiatric medicine [7].

1.3 Importance of metals and materials in different medical fields

Metal and materials play an important role in modern medicine, re-establishing function and assisting recovery for those who have been injured or diagnosed with a disease. In medical applications, natural or synthetic biomaterials are used to sustain, augment, or replace damaged tissue or biological processes. Biomaterials have been used since antiquity, when ancient

Egyptians used animal sinew sutures as sutures. Tissue engineering, regenerative medicine, and other advances have propelled the discipline forward dramatically in the last decade.

Metals and different materials are being used in orthopaedics since last century. The development of metallic engineering in last century produced various biocompatible alloys, including stainless steel, cobalt chromium alloys, titanium alloys etc. Plates, screws, and nails that can be used to fix the bone were devised using those materials, which revolutionized fracture care. Injuries that were once treated by suspending the limb in traction for a month or by wrapping the injury in a heavy cast were now treated by internal fixation. More refined biocompatible metal alloys, such as cobalt chrome alloys, are now the primary material used for artificial joints, which require permanent implantation. The development of chemical engineering has also produced polymeric material, such as ultra-high molecular weight polyethylene (UHMWPE) or polymethylmethacrylate (PMMA), which have been gradually employed as bearing materials and bonding materials for artificial joints. Bioinert ceramics such as aluminium oxide or zirconium oxide rank as one of hardest materials found in the earth. These materials are now also used as bearing material in joint replacements [8].

Materials used in dentistry are very similar to those used in orthopaedics, since teeth are similar to bone and are anchored in bone. Dental biomaterials include metals, polymers, ceramics, and composites. Using these materials is to either prevent or fix problems, and different from the application of most other biomaterials, some of dental biomaterials are visible and hence matching the colour of the surrounding tissue can be important [9].

Pain presents a unique challenge due to the complexity of the biological pathways involved in the pain perception, the growing concern regarding the use of opioid analgesics, and the limited availability of optimal treatment options. The use of biomaterials and regenerative medicine in pain management is being actively explored and showing exciting progress in improving the efficacy of conventional pharmacotherapy and as novel non-pharmacological therapy for chronic pain caused by degenerative diseases. Regenerative therapies have been developed to repair damaged tissues in back, joint, and shoulder that lead to chronic and inflammatory pain. Novel regenerative biomaterials have been designed to incorporate biochemical and physical pro-regenerative cues that augment the efficacy of regenerative therapies. Targeting endosomal receptors by nanoparticles has shown promising anti-nociception effects. Biomaterial scavengers are designed to remove proinflammatory reactive oxygen species that trigger nociceptors and cause pain hypersensitivity, providing a proactive approach for pain management [10].

Trace metals are inorganic micronutrients that are required, by humans, in very low concentrations. They act as cofactors for the proper functioning of many enzymes and other proteins. Their deficiency leads to specific signs and symptoms. Sometimes trace metals

deficiency is not dietary, but is due to defects in intestinal absorption, transport, or recycling. Direct measurement of trace metals or other tests such as enzyme assays and molecular testing are used to confirm the clinical suspicion of trace metal deficiency. Trace metals that are necessary for our body are zinc, copper, molybdenum, manganese, and selenium etc [11].

Ophthalmology is a field that has rapidly advanced as a result of the development of new techniques and materials. Eye implants are used to restore functionality of cornea, lens, vitreous humor etc. when they are damaged or diseased. Biomaterials are an important component of the procedures that are used to improve and maintain vision. These biomaterials include visceolastic solutions, intraocular lenses, contact lenses, eye shields, artificial tears, vitreous replacements, correction of corneal curvature and scleral buckling materials [12].

Cardiovascular disease physically damages the heart, resulting in loss of cardiac function. Medications can help alleviate symptoms, but it is more beneficial to treat the root cause by repairing injured tissues, which gives patients better outcomes. A multitude of biomaterials are used in the repair and replacement of impaired heart tissues. These biomaterials fall into two main categories: synthetic and natural. Synthetic materials used in cardiovascular applications include polymers and metals. Natural materials are derived from biological sources such as human donor or harvested animal tissues. Synthetic biomaterials are for shunts, vascular grafts, mechanical heart valve, stents etc [13].

A wide variety of biomaterials are used in the central nervous system (CNS): drugs or gene carriers for treatment of neurological disorders and brain tumours, scaffolds for promoting tissue regeneration, neural electrodes for restoration of lost neurological functions or shunt systems for hydrocephalus. The biomaterials used in the CNS include silicone, lipids, natural polymers and synthetic polymers in various forms based on their applications. Biomaterials can be categorized as biodegradable or non-biodegradable, depending on their fate after implantation or injection. Some applications, such as neural electrodes or CNS shunts, require the biomaterials to remain functional indefinitely. Other applications, such as drug carriers or tissue scaffolds, require the biomaterials to degrade after their function is fulfilled [14].

These metal and materials (ceramic, polymer, composite etc.) have tremendous scope in medical science. so many researches are going on in these materials to improve its characteristics and applications in human body and many data, theories are available discretely. Perhaps there is no comprehensive study of applications and importance of these metal and materials available. so, the purpose of doing this project is to make a comprehensive study of importance of these metal and materials in medical science.so we will first find out how these materials are used in recent time and advancement in each and every field of medical science and what are the advantages and disadvantages of these materials after applications in human body. Then we will find out

how to overcome these limitations by technological advancement and will try to upgrade the material for the benefits of society and medical science. we will also try to identify the novel area of each field of medical science.

Chapter 2: Literature review

2.1 Advancement of materials in orthopaedic

Bone and joint degenerative and inflammatory problems affect millions of people worldwide. In fact, they account for half of all chronic diseases in people over 50 years of age in developed countries. In addition, it is predicted that the percentage of persons over 50 years of age affected by bone diseases will double by 2020.These diseases often require surgery, including total joint replacement in cases of deterioration of the natural joint. Besides, numerous bone fractures, low back pain, osteoporosis, scoliosis and other musculoskeletal problems need to be solved by using permanent, temporary or biodegradable devices. Therefore, orthopaedic biomaterials are meant to be implanted in the human body as constituents of devices that are designed to perform certain biological functions by substituting or repairing different tissues such as bone, cartilage or ligaments and tendons, and even by guiding bone repair when necessary [15].

During most of the twentieth century, the availability of materials for the elaboration of implants was the same as for other industrial applications. Indeed, pioneer surgeons designed their implants using materials available and with a successful record of industrial use such as in chemistry, energy, mechanical and aerospace. Since the human body consists of a highly corrosive environment, very stringent requirements are imposed on the candidate materials' properties. Consequently, the first generation of biomaterials consisted of easily available materials of industrial use, that were required to be as inert as possible in order to reduce their corrosion and their release of ions and particles after implantation. Mechanical properties also play a leading role in the selection of candidate materials for implant manufacture. The concept of biocompatibility, associated with a set of in vitro and in vivo standardized tests, was introduced in order to assess the biological behaviour of synthetic materials [16].

2.1.1 *Titanium alloys in orthopaedic*

The use of biomaterials dates back to antiquity, with animal tissue being used by the Egyptians as a suture to seal wounds. In ancient Phoenicia, artificial teeth were attached to normal teeth using gold wire. The titanium was discovered in 1791 by mineralogist William Gregor, a discovery that would later prove to revolutionize the field of orthopaedic biomaterials. However, the earliest recorded attempts at hip replacement occurred in 1891 and used ivory to replace the femoral heads of patients whose hip joints had been damaged by tuberculosis. It was not until the mid-twentieth century that the modern interpretation of the metallic hip implant came into fruition, with Sir John Charnley pioneering the modern hip replacement in the 1960s. Since then, the global orthopaedic implant market has grown substantially and is forecasted to hit USD 8.97 billion by 2025 [17].

2.1.1.1 Titanium grades:

Titanium exists in many distinct phases and alloys; therefore, it is not surprising that it can be classified into a variety of different ways. Firstly, titanium and its alloys may be divided into different grades. Around forty to fifty grades are in use, although only a select few are recognized and specified by the American Society for Testing and Materials (ASTM). Commercially pure titanium (cp-Ti) is defined as titanium that consists of <1% of other alloying elements. Cp-Ti constitutes the first four grades of titanium and differ in their impurity. content and metallurgic properties. Common impurities include carbon, iron, and oxygen, which are introduced during the manufacturing process. Cp-Ti is generally lower in strength than the higher, alloyed grades. The most common alloyed grade is grade 5, which is Ti6Al4V. Ti6Al4V has excellent biocompatibility coupled with superior mechanical properties, and it alone makes up more than 50% of all titanium alloys used commercially.

	% of Impurity Present					Tensile Strength (MPa)
ASTM Grade	N	C	H	Fe	O	
1	0.03	0.1	0.015	0.2	0.18	240
2	0.03	0.1	0.015	0.3	0.25	345
3	0.05	0.1	0.015	0.3	0.35	450
4	0.05	0.1	0.015	0.5	0.40	550
5	0.05	0.08	0.0125	0.25	0.13	860

Table 2.1: Properties of Titanium Grades 1–5 from ASTM F 67 and ASTM F 136

2.1.1.2 Titanium phases:

Another classification system is based on that fact that pure titanium can be found as two distinct allotropes. At lower temperatures titanium exists in a-phase, which has a closed hexagonal crystal structure; however, above 883C it exists in β-phase, which has a body centred cubic structure. The temperature at which titanium moves from the a-phase to the β-phase is known as the β -transus temperature. By modifying the elemental composition of titanium alloys, the β -transus temperature may be altered. α -stabilizers (Al, N, O) increase the β -transus temperature, whereas β -stabilizers (V, Nb, Cr, Fe) reduce the β -transus temperature. Neutral stabilizers (Sn, Zr) have negligible effect on the temperature at which allotropic transformation occurs. Titanium alloys can be classified into several categories based on their crystalline form. α-alloys contain predominantly a-stabilizers, near-a alloys contain 1%–2% β -stabilizers, α - β alloys contain 10%–30% β -phase upon heating, and metastable- β alloys consist predominantly of the β -phase. The different categories of titanium all possess their own unique metallurgic properties that can be exploited for use in the biomedical

setting. α -alloys possess excellent corrosion properties; However, they have relatively low tensile strength compared with α - β and β -alloys. α -alloys do however possess higher creep strength than their α - β alloy counterparts. a-alloys are primarily used in the chemical and engineering industry as their properties are more suited within that sector. The majority of titanium alloys used within the biomedical field are either α - β or metastable- β alloys, as they tend to satisfy most of the characteristics desired for an implantable medical device. Ti6Al4V and Ti6Al7Nb are regarded as two of the most commonly used titanium α - β alloys in practice. It is therefore understandable as to why a great deal of attention has recently been focused into the investigation of metastable β Ti alloys with the intention of discovering novel approaches to improve in vivo performance of titanium-based medical devices [18].

2.1.2 Applications of titanium in orthopaedic

The manufacturing of titanium products has advanced substantially following the end of the second world war, and titanium has now been commonplace for use in the biomedical industry for well over half a century. Titanium's impressive tribological properties and ability to Osseo integrate make it an attractive candidate for a variety of clinical applications including maxillofacial surgery and point prostheses. One of the most notable uses is the artificial hip, which consists of several components, each made with a different material with corresponding desirable properties that meet the functional needs of that component. Titanium is often used as the femoral stem but can also be used in other components.

Alternative clinical uses for titanium include knee replacements, in which titanium is used to replace the autogenous tibial component of the joint. Dental and maxillofacial applications include replacement of missing teeth in edentulous patients using titanium to act as a screw to hold the prosthesis in place or plates and screws to repair maxillofacial deformities and traumatic injuries. Titanium's use as an implanted medical device is incredibly diverse ranging from pacemakers to even cochlear implants. Currently 70%–80% of all implant materials currently used are metallic, many of which are fabricated from titanium.

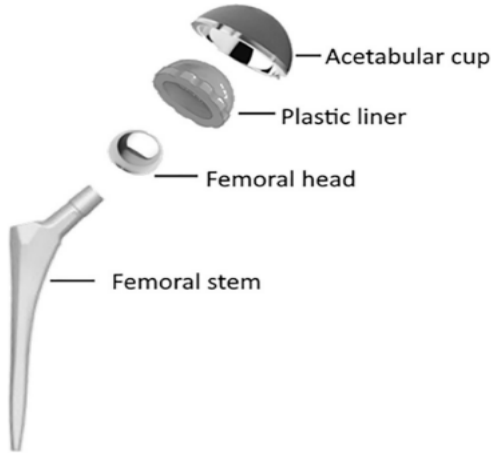

Figure 2.1: Components of a Total Hip Arthroplasty

2.1.3 Advancement of titanium in orthopaedics

To increase an orthopaedic implant's lifetime, research trends have included the development of new titanium alloys made of nontoxic elements with suitable mechanical properties (low Young's modulus – high fatigue strength), good workability and corrosion resistance. In order to prevent undesirable events, In order to avoid such undesirable events, innovative solutions arising from tissue engineering and materials and surface sciences focus on reaching a solid initial anchorage of the prosthesis (preferentially through biomimetic alternatives); a reduction of the friction coefficient of the coupling of materials so that toxic particles are not released; and finally, continuous elasticity between bone and implant in order to minimize stress shielding.

Thus, to promote osseointegration of implants, hybrid artificial organs, also known as bioartificial organs seem to be a promising concept depending upon which it is possible to build in vitro functional units made of artificial materials and living cells. To achieve a quick and stable building of these functional units, enabling a rapid cell colonization of the artificial materials, mainstream approaches involve the surface immobilization of peptides, proteins or growth factors onto biomaterial. For instance, since the identification of the Arg–Gly–Asp (RGD) sequence as mediating the attachment of cells to several plasma and extracellular matrix (ECM) proteins (e.g., fibronectin and vitronectin), researchers have been depositing RGD-containing peptides on biomaterials to promote cell attachment.

There are certain properties and mechanical requirement for designing a new titanium alloy. In the consideration of implants, of outstanding importance is device stiffness, which can be defined as the product of the moment of inertia and of Young's modulus. A low stiffness as close to that of the natural bone as possible provides a good load transfer whereby the stimulation of new bone formation is realized. While stress shielding (high stiffness) results in bone resorption, a low stiffness

under static and/or dynamic loading will provide an elastic elongation of the cells in the vicinity of the implant, whereby the production of calcium, which is the basis of bone formation, is stimulated. In the region of physiologic stress and strain, respectively, bone formation and resorption are balanced. A decrease in the stress in this region causes resorption, which decreases the cross section of the bone, whereby stress and bone formation are increased until equilibrium is again achieved.

the motivation to develop lower modulus alloys has led to an increased focus on metastable β-Ti alloys, since Young's moduli of β-type Ti alloys are recognized to be much smaller than that of α–β-Ti alloys, especially Ti6Al-4V. For instance, the TiO steum β alloy (Ti-35.3Nb4.9Ta-7.2Zr) exhibits a Young's modulus corresponding to 55 versus 105 GPa for Ti-6Al-4V. Numerous Ti-Nb-Zr-Ta alloys have been designed for the last 10 years either in USA or in Japan. This quaternary system benefits from containing only nontoxic metallic alloying elements. In the USA, in the middle of 1990s, Ahmed and Rack developed many compositions belonging to the Ti-Nb-Ta-Zr system. In total, 28 Ti-alloys were then produced consisting of between 2.5 and 13% by weight Zr, 20 and 40% by weight Nb, 4.5 and 25% by weight Ta and the balance Ti. This trial-and-error series of experiments furnished the relationship between the chemical composition of these 28 alloys and their elastic modulus; all moduli are found below 65 GPa. Their three preferred alloys were Ti-23.8Nb-21.6Ta-4.6Zr, Ti-29.2Nb-12.4Ta-7.1Zr and Ti-35.3Nb-5.7Ta-7.3Zr. Conversely, in Japan, Niinomi's group developed a new β-Ti alloy (Ti-29Nb-13Ta-4.6Zr) under the guidance of the abovementioned DV–Xa cluster method. Since 1998, they have intensively studied the relationship between mechanical properties and microstructure and thus, shown that the fatigue limit (770 MPa) of this alloy aged 723 K after cold rolling is nearly equal to that of hot-rolled Ti-6Al-4V ELI. On the basis of the abovementioned theoretical studies, as well as experimental information, the Ti-6.5Mo-6Mn-1.5Fe-1.5Al composition was retained. Particular attention could be paid to Mn, Fe and Al concentrations. Since a small addition of Mn appears to greatly enhance the admissible strain, 6 wt.% of Mn was introduced into the alloy composition. Finally, while considered as potentially cytotoxic, Al was added in a small amount to stabilize the secondary α phase. The first studies have confirmed the general biocompatibility of Ti-6.5Mo-6Mn-1.5Fe-1.5Al [19].

2.1.4 Stainless steel alloy in orthopaedic

Since the development of stainless steels over a century ago, they have made significant contributions to the health of humankind. Stainless steels are a family of cost-effective engineering materials with good corrosion resistance and a suitable range of mechanical and physical properties that are applicable to a wide variety of load-bearing implant applications. The first stainless steel utilized for implant fabrication was the 18-8 (type 302 in modern classification), which is stronger and more resistant to corrosion than the vanadium steel. Vanadium steel is no longer used in implants since its corrosion resistance is inadequate in vivo. Later 18-8sMo stainless steel was introduced

which contains a small percentage of molybdenum to improve the corrosion resistance in chloride solution (salt water). This alloy became known as type 316 stainless steel. In the 1950s the carbon content of 316 stainless steel was reduced from 0.08 to a maximum amount of 0.03% (all are weight percent unless specified) for better corrosion resistance to chloride solution and to minimize the sensitization, and hence became known as type 316L stainless steel. The minimum effective concentration of chromium is 11% to impart corrosion resistance in stainless steels. The chromium is a reactive element, but it and its alloys can be passivated by 30% nitric acid to give excellent corrosion resistance [20].

2.1.5 Advancement of Stainless-steel alloy in orthopaedic

The austenitic stainless steels, especially types 316 and 316L, are most widely used for implant fabrication. These cannot be hardened by heat treatment but can be hardened by cold-working. This group of stainless steels is nonmagnetic and possesses better corrosion resistance than any others. The inclusion of molybdenum enhances resistance to pitting corrosion in salt water. The only difference in composition between the 316L and 316 stainless steel is the maximum content of carbon, i.e., 0.03%. The nickel stabilizes the austenitic phase [γ, face centred cubic crystal (FCC) structure] at room temperature and enhances corrosion resistance. The austenitic phase formation can be influenced by both the Ni and Cr contents as shown in Fig.2.2 for 0.10% carbon stainless steels. The minimum amount of Ni for maintaining austenitic phase is approximately 10%. The properties of different conditioned stainless steel are given in table 2.2.

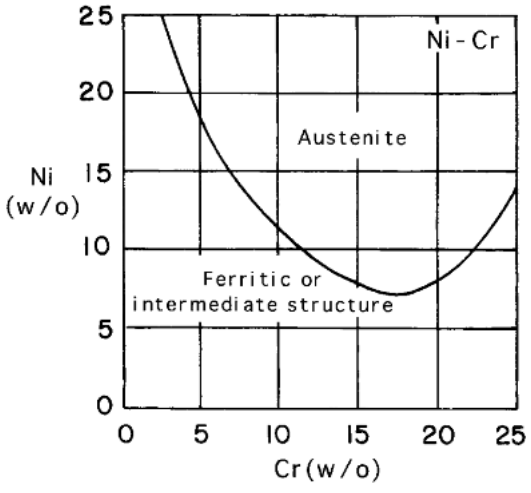

Figure 2.2- The effect of Ni and Cr contents on the austenitic phase of stainless steels containing 0.1% C

Condition	Ultimate Tensile Strength, min. (MPa)	Yield Strength 0.2% offset), min.	Elongation 2 in. (50.8mm), min. (%)	Rockwell hardness
Annealed	485	172	40	95 HRB
Cold worked	860	690	12	

Table 2.2: mechanical properties of 316L stainless steel

A wide range of properties exists depending on the heat treatment (annealing to obtain softer materials) or cold working (for greater strength and hardness). Figure 2.3 shows the effect of cold working on the yield and ultimate tensile strength of 18-8 stainless steels. The engineer must consequently be careful when selecting materials of this type. Even the 316L stainless steels may corrode inside the body under certain circumstances in a highly stressed and oxygen depleted region, such as the contacts under the screws of the bone fracture plate. Thus, these stainless steels are suitable for use only in temporary implant devices such as fracture plates, screws, and hip nails. Surface modification methods such as anodization, passivation, and glow-discharge nitrogen implantation are widely used in order to improve corrosion resistance, wear resistance, and fatigue strength of 316L stainless steel.

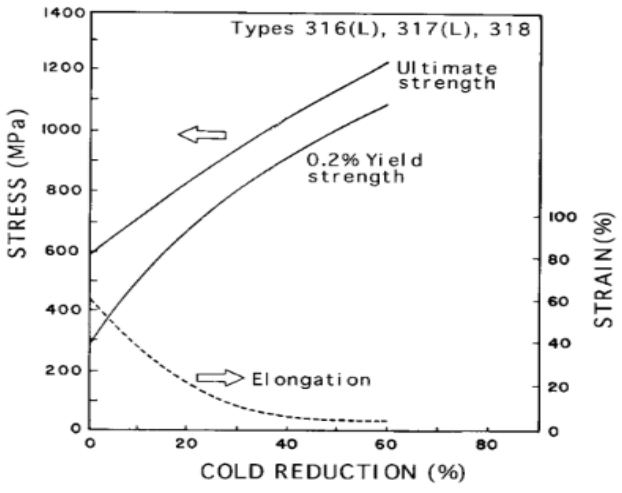

Fig 2.3: Effect of cold-work on the yield and ultimate tensile strength of 18-8 stainless steel

In the 1980s, stain-less steels with improved mechanical properties and superior corrosion resistance compared to 316L have appeared. These alloys contained higher amounts of Cr, manganese (Mn), and nitrogen (N) than 316L. Rex 734 is an example of this alloy, which is used for manufacturing

hip stems. Subsequently, in response to concern about patients' sensitivity to Ni, a new generation of implantable stainless steels containing very low Ni content was developed. These low-Ni alloys contain higher amounts of Mn and N to stabilize the desired austenitic phase. Among numerous alloys that belong to the families of stainless steel, only austenitic and precipitation-hardened (PH) stainless steels are used as orthopaedic biomaterials. On the other hand, martensitic stainless steels with excellent hardness are ideal for surgical instruments. Besides the families of stainless steels in which the alloying elements play a significant role in their suitability for orthopaedic implant applications, it is important to ensure low content of non-metallic inclusions in the fabricated devices with the aid of vacuum melting. Non-metallic inclusions are undesirable compounds since they act as stress-concentration points that deteriorate the mechanical properties (especially fatigue strength) of the devices. After final shaping, medical devices and implants are often ground and polished to obtain the desired surface roughness, followed by passivation treatment (commonly via exposure to a 40% HNO_3) solution or thermal oxidation treatment—ASTM F86). Thus, the most commonly used stain-less steel in orthopaedic practice is denoted as AISI 316LVM [21].

2.1.7 Applications of stainless steel in orthopaedic

a) stainless steel is suitable for use as temporary implants like bone plates, hip nails, screw.

2.1.8 Advancement of cobalt chromium alloys in orthopaedics

Cobalt-based alloys have been used in demanding applications for as long as investment casting has been available as an industrial process. Cobalt-chrome (Co-Cr) is a metal alloy of cobalt and chromium. Because of its great strength, temperature tolerance, and wear resistance, it is commonly used in dental and orthopaedic implants. The increased stability and excellent material properties of Co-Cr alloys are advantageous for long-term durability and thus are a promising advance for younger patients in need of total joints. The alloy composition used in orthopaedic implants (ASTM-F75) is composed of cobalt with 27–30% chromium, 5–7% molybdenum, and traces of manganese and silicon (<0.1%) (<0.75%), nickel (<0.5%), and carbon, nitrogen, tungsten, phosphorus, sulphur, and boron. Cobalt-chromium-molybdenum (Co-Cr-Mo) alloys are especially useful where high stiffness or a highly polished and extremely wear-resistant material is required. It can be used in gas turbines, valve seats, nuclear power plants, automotive engines, aerospace fuel nozzles, engine vanes, and various components, but most importantly it can be used in a variety of orthopaedic and dental implants due to its high biocompatibility. Co-Cr-Mo alloys are widely used for medical prosthetic implant devices, such as knee implants, metal-to-metal hip joints, and dental prosthetics. Cobalt-

nickel-chromium-molybdenum (Co-Ni-Cr Mo) alloys are also used for implants. Because of the possible toxicity of released Ni ions from Co Ni-Cr alloys and their limited frictional properties, Co-Cr-Mo is usually the dominant alloy for total joint arthroplasty.

Co-Cr alloy in orthopaedic surgery is well tolerated. Nevertheless, it is still considered less biocompatible than Ti. A study explored the biocompatibility of Co-Cr-Mo by investigating the biomechanical implant fixation and implant osseointegration of Co-Cr-Mo (ASTM F-75) porous bead-coated and Ti (ASTM F-136) porous bead-coated implants in an animal model. In 10 dogs, the two implant types were inserted into the proximal part of the humerus. Implant sites were over drilled, leaving an empty 0.75-mm gap between implant and surrounding bone. The implants were observed for 6 weeks and were evaluated by biomechanical push-out test and histomorphometry. The authors found a statistically significant 40% decrease in the biomechanical fixation of Co-Cr-Mo porous bead-coated implants compared with Ti porous bead-coated implants that could be critical for long term performance. Implant osseointegration was comparable between the two implants; however, a slight decrease in bone volume density around CoCr-Mo implants was observed [22].

2.1.8 Applications of cobalt chromium in orthopaedic

a) femoral component in total knee replacement and femoral head in total hip replacement

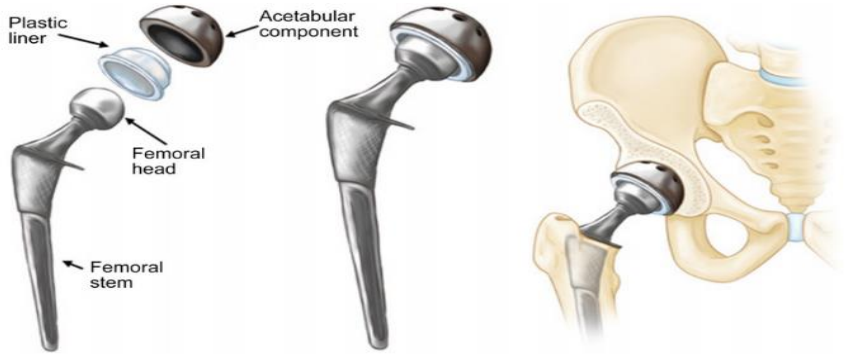

Figure 2.4: Femoral component

b) screws in trauma plating systems

Figure 2.5: screws in trauma plating systems

2.1.9 Advancement of polymer in orthopaedics

Every year, tens of millions of people all over the world suffer from bone damage, most often, bone fractures, and one fifth of the victims needs hospitalization. Many of people suffer from the pathology of bone destruction as a result of osteoporosis, and about 30 million people are in the high- risk group owing to loss of bone mass. More-rare, but still sufficiently widespread, are the cases of genetically specified osteopsathyrosis and osteosarcoma. Furthermore, the need to reduce or replace bones appears in the arthroplasty of joints, vertebral arthrodesis.

Although, at first glance, polymers seem to be incompatible with such a complex structure as bone tissue in terms of biochemical and biomechanical properties, already at the first stages of innovation in this field of medicine, they have received widespread attention from bioengineers, surgeons, chemists, and physicists engaged in the creation of new materials. Precisely polymers make it possible to change in a wide range the properties of materials through variation in their composition and structure. Initially, the use of polymers evoked interest associated with the possibility to replace heavy metal parts of endoprostheses with lightweight polymeric parts. However, during the last few decades, homo and copolymers, as well as composite materials produced on their basis, have occupied an important place in the Endo prosthetics of bone lesions. The directions that are of main interest for possible applications of implants in bone systems are as follows: the Endo prosthetics of removed bones, the use of fasteners and glues for joining of bone parts or for fastening in a bone–prosthesis system, and the packing of bone defects.

2.1.9.1 Nondegradable Polymeric Implants

Endoprostheses of bones functioning in the body for life are fabricated from polymeric materials resistant to biodegradation. In this case, the main difficulties are associated with the permanent mechanical action of a device on surrounding tissues. Specifically, they are caused by its slip in a tissue medium that brings about hampered formation of a normal capsule, disturbances in metabolic processes, and necrotic changes. The improvement of engraftment of an implant resistant to biodegradation may be achieved via its nonspecific functionalization through endowment of porosity or via perforation of a material; this circumstance facilitates the intergrowth of new tissue into the implant mass and the formation of a normal tissue capsule. PMMA, polyolefins (PE and PP), polytetrafluoroethylene, PET, and PU belong to the group of wide spread biologically inert medical polymers. However, at the first stages of development in this area, only commercially available polymers were applied. Engineering polymers became the first macromolecular substances that were employed as materials of spare parts for human. It is important that these materials should preserve their properties during the entire period of function because the physiological medium of the body may be considered sufficiently aggressive. This requirement is fulfilled owing to the stability of chemical bonds constituting back bones of the mentioned polymers, specifically, carbon–carbon or silicon–oxygen bonds, and owing to the hydrophobicity of macromolecules that prevents penetration of water into the material.

2.1.9.2 Biodegradable polymeric implants

Implants based on these polymers temporarily function in the body and are replaced with the regenerated bone tissue during destruction. Such polymers are most frequently used to manufacture fastening elements of bone fractures and certain types of glue compositions and to replace bone elements able for rapid regeneration. Polyesters of hydroxycarboxylic acids and polymers of cyanoacrylates are the main types of synthetic biodegradable polymers suitable for the design of implants. Thus, a number of polymeric materials have already found diverse applications in orthopaedic surgery. It is important to note that polymers, whose properties may be altered in a wide range, depending on their chemical composition and structure, have made it possible to create implants and devices improving the quality of life of patients. However, it is evident that many problems exist, the main of which is the reaction of the body to the introduction of alien objects [24]. Moreover, all modern orthopaedic implants lack three of the most important characteristics of living tissues: namely, self-healing capability and the abilities to maintain the blood supply and to change the structure and properties in response to the environment. In addition, the growing demand for long term orthopaedic recovery suggests the dis placement of emphasis from the replacement of tissues to their regeneration [23].

2.1.10 Applications of polymer in orthopaedic

a) Acetabular liner

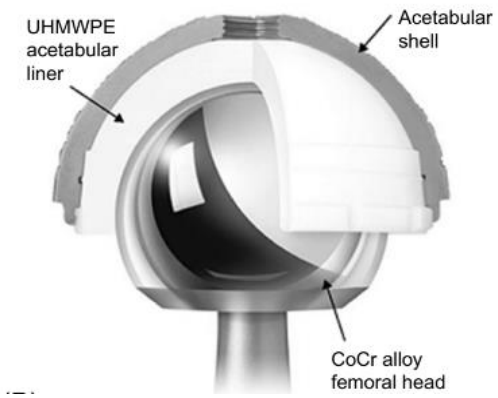

Figure 2.6: Acetabular liner

b) Tibial insert

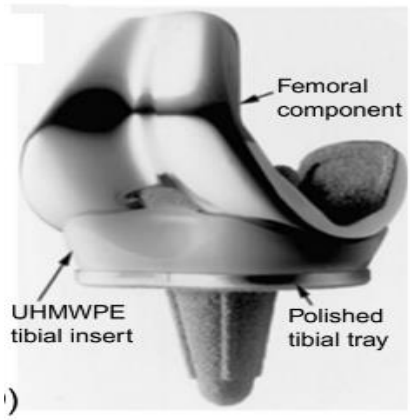

Figure 2.7: Tibial insert

2.1.11 Advancement of ceramic in orthopaedic

Ceramics are non-metallic inorganic materials with a broad range of composition. They are usually processed by mixing the particulates of the material together with water and an organic binder. The mixture is then pressed into a mould to obtain the desired shape, dried to evaporate the water and

the binder burned out by thermal treatment. Firing or sintering at a very much higher temperature then densifies the residual material. The final microstructure of the ceramic is greatly dependent on the thermal process applied, the maximal temperature reached and the duration of the thermal steps. There are five types: glass, plasma sprayed polycrystalline ceramic, vitrified ceramic, solid state sintered ceramic and polycrystalline glass-ceramic. Other factors such as the purity of the powder, the size and distribution of the grains, and the porosity are important in determining the mechanical and biological properties. The extended use of bio-ceramics in medicine is related to their excellent bio-compatibility as a result of their high level of oxidation.

Ceramics used in orthopaedic surgery are classified as bioactive or inert according to the tissue response when implanted in an osseous environment. The bioactivity of a material can be defined as its ability to bond biologically to bone. An inert ceramic merely elicits a minor fibrous reaction. In clinical practice, inert fully-dense ceramics are used as bearings in total joint replacements because of their exceptional resistance to wear and their tribological properties. By contrast, bioactive ceramics are employed as coatings to enhance the fixation of a device or as bone-graft substitutes because of their osteoconductive properties.

2.1.11.1 Sliding ceramic

Sliding ceramics. The most widely used bearing couple in total joint replacements remains metal-on-polyethylene. The long-term survival of the artificial joint, however, is impaired by the wear of its components which ultimately leads to osteolysis around the implant secondary to an inflammatory response induced by wear debris occurring from both the articulating and non-articulating surfaces. Of the different types of particles found in the membranes surrounding the loosened components, polyethylene debris has been identified as a major factor inducing activation of macrophages which leads to the production of bone-resorbing cytokines with resultant loss of bone stock, especially in the young and active population. They are mainly used in total hip arthroplasty as femoral heads articulating against polyethylene, and as cups in the alumina-on-alumina combination.

2.1.11.2 Alumina ceramic

Dense alumina of surgical grade is obtained by sintering alumina powder at temperatures between 1600 and 1800°C. The resultant material is in its highest state of oxidation, allowing thermodynamic stability, chemical inertness and excellent resistance to corrosion. Improvement in the manufacturing

process has lowered the size and distribution of the grains, which are major factors in avoiding the propagation of cracks and fracture. Alumina is a brittle material with excellent compression strength but the bending strength is limited. The Young's modulus is 300 times greater than that of cancellous bone, and 190 times higher than polymethylmethacrylate (PMMA). Alumina has been a standardised material since 1984 (International Standard Organisation, ISO 6474).

2.1.11.3 Zirconia ceramics

manufacture of femoral heads for total hip replacements because of its higher strength and toughness which would reduce the risk of fracture. Pure zirconia is an unstable material showing three different crystalline phases: monoclinic, tetragonal and cubic. The phase changes result in a large variation in volume and significantly decrease the mechanical properties of the material due to the production of cracks. Stabilisation of zirconia by adding oxides to maintain the tetragonal phase has therefore been under taken. Yttrium-stabilised tetragonal polycrystalline zirconia (Y-TZP) has a fine grain size and offers the best mechanical properties. This material was standardised in 1997 (International Standard Organisation, ISO 13356). Zirconia femoral heads should articulate only against polyethylene sockets since both zirconia against alumina and zirconia

2.1.11.4 mixed oxide ceramic

A new class of materials has been developed recently to combine the tribological properties of alumina and the mechanical characteristics of yttrium stabilised zirconia. These mixed-oxide ceramics containing 40% to 80% zirconia have shown rates of wear in vitro comparable to those of alumina ceramic. Preliminary results in hip joint simulators have been promising, but further investigations are needed to assess their long-term.

2.1.11.5 Bioactive ceramics

Bioactive ceramics are osteoconductive, acting as a scaffold to enhance bone formation on their surface, and are used either as a coating on various substrates or to fill bone defects. An osteoconductive material can only elicit bone formation in an osseous environment, whereas an osteo-inductive substance can promote bone formation even in an extraosseous situation

2.1.11.6 Calcium phosphate ceramic

Two bio-ceramics belonging to the calcium phosphate family have had extensive evaluation as orthopaedic implants, namely HA and tricalcium phosphate (TCP). Stochiometric synthetic HA ($Ca_{10}(PO_4)_6(OH)_2$), with a calcium-to-phosphate atomic ratio of 1.67, was introduced as a bone-graft

substitute because its formula is similar to that of the inorganic mineral phase of bone. Biological HA, however, is Ca deficient and a carbonated apatite. The bonding mechanism of HA to bone, although not completely understood, seems to be due to the attachment at the surface of the HA of osteogenically-competent cells which differentiate into osteoblasts. A cellular bone matrix is then formed at the surface of the HA. An amorphous area is present between the surface and the bone tissue containing thin apatite crystals. As maturation occurs, this bonding zone shrinks and HA becomes attached to bone through a thin epitaxial layer, resulting in a strong interface with no layer of fibrous tissue interposed between the bone and HA. Bone formation grows from the surface of the HA towards the centre of the pores. HA coating is widely used on femoral prostheses and on sockets as a means of fixation in order to avoid complications related to the use of PMMA.

2.1.11.7 Bioactive glasses

They bond chemically to bone. The model in this class of materials is Bio-glass 45S5 of which the composition in weight % is: 45% SiO_2, 24.5% CaO, 6% P_2O_5 and 24.5% Na_2O. The bonding mechanism of silicate bioactive glasses to bone has been attributed to a series of surface reactions ultimately leading to the formation of a hydroxycarbonate apatite layer at the glass surface. The critical element necessary for the formation of this is the production of a layer of porous silica gel with a high surface area. Greater production of bone has been demonstrated with Bio-glass 45S5 when compared with HA

2.1.11.8 Bioactive bone ceramic

Bioactive bone cements have been explored as an alternative to PMMA in order to avoid complications related to PMMA debris and to enhance fixation of the prosthesis. These materials have undergone extensive basic research. They include calcium-phosphate based bone cement and glass-ceramic bone cement. A strong cement-bone interface is obtained by the formation of HA at the surface of the cement. Moreover, calcium phosphate cements are resorbable and are progressively replaced by newly-formed bone. To our knowledge, however, clinical trials of such materials have not yet been undertaken. The excellent biocompatibility and outstanding tribological properties of inert ceramics have encouraged their use as bearings in total joint replacements. Improvement in the manufacturing process has allowed the production of reliable materials. They are best used in young and active patients who have a high risk of loosening and osteolysis in the mid to long term. Ceramic coatings provide an attractive alternative for biological fixation. In the near future, ceramic substitutes for bone grafts will probably be used in association with osteoinductive materials such as bone morphogenetic proteins or mesenchymal stem cell accelerate bone formation further [24].

2.1.12 Advancement in dental material

Biomaterials used in dentistry are very similar to those used in orthopaedics, since teeth are similar to bone and are anchored in bone. Dental biomaterials include metals, polymers, ceramics, and composites. Using these materials is to either prevent or fix problems, and different from the application of most other biomaterials, some of dental biomaterials are visible and hence matching the colour of the surrounding tissue can be important. Metals are often used as anchors in dental implants. They provide the strength needed to hold the implant in the bone under the stresses that the mouth goes through. The metals include titanium and its alloys, cobalt-based alloys and stainless steel. Dental crowns and bridges can also be made of metal. Gold crowns are common. Dental amalgam, which is composed of mercury, copper, tin, zinc, and silver, is used as a filler material for cavities after tooth decay. Bio-ceramics are common dental biomaterials. In some cases, they can be used as the anchors of implants as well. Some bio-ceramics, for example, medical grade alumina, have the high strength needed in the mouth and have low thermal conductivity, while exhibiting a colour similar to natural teeth. Calcium phosphates including HA are also commonly used. HA can be coated on metal implants to promote osteointegration with bone. Polymers are used mostly as cements or fillers in dentistry. Cements or fillers start out as liquids and/or solid powders and are hardened to hold two solids together or fill holes. Some harden on their own after mixing, while others need to be hardened, for example, by UV light. They are usually made by mixing solid and liquid components. There are cements made of zinc phosphate, zinc polycarboxylate, glass ionomers such as calcium and aluminium silicate, resins such as urethanes, and other types that can be used for specific purposes. All dental biomaterials must survive the harsh and fluctuating conditions of the mouth. They are hard and stable material that work together in multiple ways. The metals, ceramics, polymers and composites work together and allow for integration with the host tissue [25].

2.1.13 Advancement of titanium in dentistry

Among various dental materials and their successful restorative uses, titanium provides an excellent example of integrating science and technology involving multiple disciplines of dentistry including biomaterials, prosthodontics and surgical sciences. Titanium and its alloys have emerged as a material of choice for dental implants fulfilling all requirements biologically, chemically and mechanically. Several excellent reviews have discussed the properties of titanium and its surface characteristics that render it biocompatible. However, in most patients, titanium implants are used alongside several other metals. Presence of different metals in the same oral environment can alter the properties of titanium. Other influencing factors include intra-oral pH, salivary content, and effect of fluorides [26].

2.1.13.1 Biological reaction with titanium surface

At present little is known about dental hypersensitivity to titanium implants. More long-term studies are warranted in order to better understand these reactions. Shibli et al. analysed the surface topography and composition of failed titanium dental implants in order to determine possible causes of failure. Results from this study do not point at any material-related causes for implant failure. A study done on hypersensitivity to titanium has shown that none of the patients had any adverse reactions. Recent clinical reports however have shown patients showing symptoms of contact derma titis or granulomatous reactions to titanium upon its use in pacemakers, hip prostheses, and even surgical clips. Additionally, the potential for adverse human tissue responses to titanium dioxide, the passivating layer that always covers the surface of titanium materials, has also been reported. Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and by the absence of B lymphocytes, indicating Type 4 hypersensitivity. Type 4 hypersensitivity reaction is a cell-mediated, delayed response that occurs hours to days after exposure to the immunogen. It involves a complex series of steps that elicit a T-cell response to the antigen. Metals like nickel, cobalt and Ti are said to induce this type of reaction. Released Ti debris may combine with biomolecules to form a protein-metal complex and become immunogenic, eliciting a T-cell mediated Type 4 response. The typical manifestations of Type 4 hypersensitivity reactions include, but are not limited to unexplained pain, contact dermatitis, atopic eczema, impaired wound healing and sterile osteomyelitis. Studies evaluating the oral tissue changes adjacent to titanium implants in patients reported no evidence of inflammatory response and no association between the identification of pigmented debris in the tissues and clinical symptoms. However, the relationship between titanium dental implants and clinically relevant hypersensitivity has been recently suggested. These reports raise the question that metal sensitivity may arise after exposure to titanium for some patients in certain circumstances. Report by Egusa et al. demonstrates the emergence of eczema localized to the perioperative facial area after receiving titanium dental implants, in which a complete remission was subsequently achieved by the removal of the titanium material. Thus, it seems that titanium can induce hypersensitivity in susceptible patients and could play a critical role in implant failure. This validation needs long-term clinical and radiographic follow-up of all implant patients sensitive to metals [27].

2.1.13.2 Applications of titanium in dentistry

Titanium has been used in cast dental prostheses since the 1970s. Equipment is available to cast titanium into single-and multiple-unit-crown-and-bridge frameworks, implant-supported structures and partial or full denture bases.

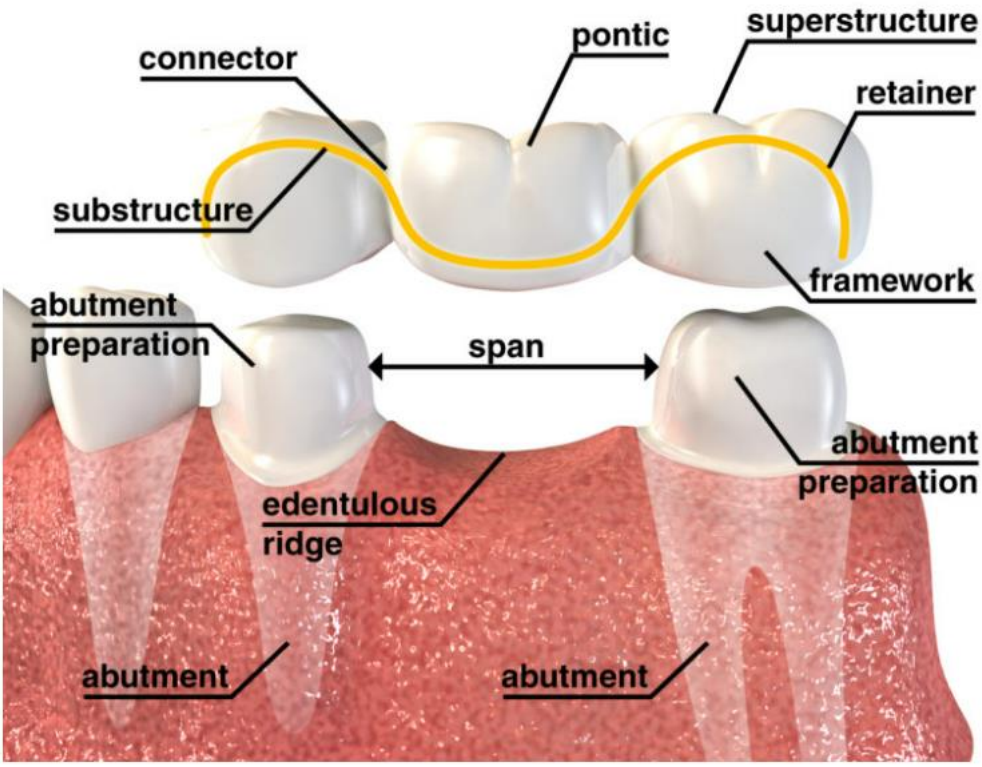

Figure 2.8: Dental crown and bridge framework

2.1.14 Advancement of cobalt chromium alloys in dentistry

During the 20th century, metal alloys have assumed an important role as restorative materials. Among existing examples, cobalt–chromium (Co–Cr) alloys increasingly began to be used in medicine and especially in dentistry. Their success is mainly due to their mechanical properties such as stiffness, strength and corrosion resistance, thus allowing a high compatibility. There are quite meaningful data on the corrosion and toxicity of Co–Cr alloys for their use in restorative materials such as dental prostheses. Toxicological studies following Co and Cr exposures in the oral cavity are more difficult to conduct because there are many different situations leading to the release of metal ions and wear particles. Furthermore, the links between exposure and the appearance of local or systemic toxicity are not automatic. Since 2017, the European Union (EU) regulatory framework

for Co–Cr alloys has been undergoing profound changes. A new EU Medical Devices Regulation (MDR) (2017/745) was applied in May 2021 with the need to consider that Co metal is a new carcinogenic, mutagenic and toxic to reproduction (CMR) substance. On 18 February 2020, the 14th Adaptation to Technical Progress (ATP14) to the Classification, Labelling and Packaging (CLP) regulation was published, including the harmonised classification for Co metal as a CMR 1B substance. In this context, the use of Co might be forbidden if the medical devices are invasive and as soon as they include more than 0.1% (m/m) Co [28].

2.1.15 Advancement in stainless steel in dentistry

Stainless steel has many uses in orthodontics for the fabrication of brackets, arch wires, bands, ligatures, among other appliances. Stainless steel is an alloy composed of iron and carbon that contains chromium, nickel, and other elements that impart the property of resisting corrosion. There are many different stainless-steel alloys in the market, some of which are useful in orthodontics due to their properties. The three main groups are austenitic, martensitic, and ferritic. Alloys used in orthodontics come from the austenitic type, being 18/8 (18% chromium, 8% nickel, 0.2% carbon and traces of other stabilizing elements) the most widely used. The widespread use of stainless steel in the medical and dental fields resides in different factors, but one of the most important features is its corrosion resistance. This property comes from the addition of chromium to the iron-carbon alloy. This base metal is highly reactive and forms a passive film. This film of chromic oxide resists further attacks from the environment, thus preventing corrosion. Around 11% chromium is necessary to produce corrosion resistance in pure iron, and the proportion increases with the addition of carbon to form the alloy. Passivation may be influenced by different factors such as alloy composition, heat treatment, surface condition, stress, and the environment in which the alloy is placed. In current orthodontic practice, professionals use stainless steel in many appliances for the various techniques. However, many of these professionals lack the proper knowledge an orthodontist should have about a material that is used on a daily basis and, hence, do not take advantage of all the remarkable properties stainless steel alloys offer. Chemical composition and AISI grades of some stainless-steel alloys are given in the table

2.1.16 Orthodontic applications of stainless-steel alloy

Orthodontic brackets: Most manufacturers of orthodontic products use different stainless-steel alloys for the fabrication of the numerous brackets they offer. Austenitic stainless steel, such as AISI 304L and 316L, remains as the first choice for the manufacturing of bracket. However, orthodontic brackets are also manufactured using alternative stainless-steel alloys, such as 17-4 pH stainless-steel and 2205 alloy.

2.1.16.1 Orthodontic mini-implants

Although most mini-implants or screws used as anchorage devices in the orthodontic field are made of titanium alloys due to this metal's outstanding characteristics, stainless steel is still used by one manufacturer. They claim that the mini-implant made of surgical grade stainless steel can be easily removed once that action has been performed since this material will not induce osseointegration, which is advantageous because a second surgical procedure will not be necessary.

2.1.16.1 Orthodontic wires

Orthodontic wires are used to move teeth with light continuous forces to correct their positions. Most orthodontic wires are fabricated from types 302 and 304 18/8 austenitic alloys. Other types of alloys, however, have been used, such as the Australian stainless-steel alloy. It was developed by Begg and Wilcox, who were seeking a light and flexible alloy with high resiliency and toughness to be used as a wire in the newly developed Begg technique. These wires are available in sizes ranging from 0.012" to 0.024" round wire and as regular, regular+, special, special+, premium, premium+, and supreme grades according to their resiliency, which increases from regular to supreme [29].

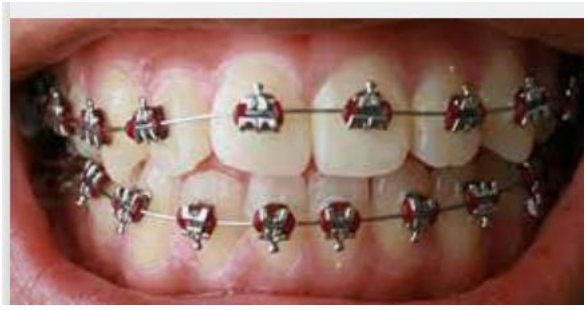

Figure 2.9: Orthodontic arch-wire

2.1.17 Advancement of ceramic in dentistry

Over the past forty years, the technological evolution of ceramics for dental applications has been remarkable, as new materials and processing techniques are steadily being introduced. The improvement in both strength and toughness has made it possible to expand the range of indications to long-span fixed partial prostheses, implant abutments and implants. The present review provides a state of the art of ceramics for dental applications. Due to the unsurpassed mechanical properties of partially stabilized zirconia, its introduction to the dental market, almost a decade ago, considerably expanded the range of applications of ceramics in dentistry, a field where they are

classically in demand due to their chemical inertness and a wide combination of optical properties, allowing excellent esthetic. Even though the current trend is toward the development of all-ceramic systems, ceramics are still widely used for veneering metallic frameworks for dental restorations. Concurrently, ceramic posts, abutments and implants are now becoming available. Dental ceramics can be classified according to their crystalline phase and fabrication technique (Table 2.3). This classification is constantly evolving with latest developments leading to the combination of several fabrication techniques and core/veneering ceramic systems, with the ultimate goal of achieving adequate strength and toughness, optimal esthetic and long-term in vivo performance [30].

	Fabrication technique	Crystalline phase
Metal-ceramics	Sintering	Leucite
	Heat-pressing on metal	Leucite, leucite & fluorapatite
All ceramics	Sintering	Leucite
	Heat-pressing	Leucite, lithium disilicate
	Dry pressing and sintering	Alumina
	Slip-casting & glass infiltration	Alumina, spinel, alumina-zirconia (12Ce-TZP)
		Alumina, alumina-zirconia (12Ce-TZP)
	Soft machining & glass-infiltration	Alumina, zirconia (3Y-TZP)
	Soft machining & sintering	Zirconia/fluorapatite-leucite glass-ceramic
	Soft machining, sintering & heat-pressing	Sanidine, leucite
		Lithium disilicate
	Hard machining	
	Hard machining & heat treatment	

Table 2.3: Crystalline phase and fabrication technique

2.1.18 Zirconia in dentistry

Due to an increasing interest in esthetics and concerns about toxic and allergic reactions to certain alloys, zirconia was proposed as a new ceramic material in the later part of 20th century. It has become a popular alternative to alumina as biomaterial and is being used in dental applications for

fabricating endodontic posts, crown and bridge restorations and implant abutments. It has also been applied for the fabrication of esthetic orthodontic brackets. This article presents a brief history, dental applications and new methods for fabrication of zirconia improving its mechanical properties. Additionally, the bonding between zirconia and resin cements as well as conventional cementation has been discussed. The methods of the improvement of the bonding strength have also been highlighted.

Zircon has been known as a gem since ancient times. The name zirconium comes from the Arabic "Zargun" (golden in colour) which in turn comes from the two Persian word "Zar" (Gold) and "Gun" (Colour). Zirconia is a crystalline dioxide of zirconium. Zirconium oxide was first used for medical purposes in 1969 for orthopaedic application. It was proposed as a new material for hip head replacement instead of titanium or alumina prostheses. Due to an increasing interest in esthetics and concerns about toxic and allergic reactions to certain alloys, patients and dentists have been looking for metal-free tooth-coloured restorations. Therefore, the development of new high strength dental ceramics, which appear to be less brittle, less limited in their tensile strength, and less subject to time dependent stress failure, has dominated in the later part of century. These capabilities are highly attractive in prosthetic dentistry, where strength and esthetics are paramount. It has become a popular alternative to alumina as biomaterial and is used in dental applications for fabricating endodontic posts, crown and bridge restorations and implant abutments. It has also been applied for the fabrication of esthetic orthodontic brackets. The mechanical properties of commercial yttria stabilized zirconia are given in Table 2.4

Mechanical properties	amount
Density	6.05 g/cm^3
Hardness	1200 HV
Bend strength	900-1200 MPa
Compressive strength	2000 MPa
Young's modulus	210 GPa
Thermal expansion	11x10^{-6} 1/k

Table 2.4: Mechanical properties of zirconia

2.1.19 Zirconia applications in dentistry

Although many types of zirconia-containing ceramic systems are currently available, only three are used to date in dentistry. These are yttrium cation-doped tetragonal zirconia polycrystals (3Y-TZP), magnesium cation-doped partially stabilized zirconia (Mg-PSZ) and zirconia toughened alumina (ZTA).

2.1.19.1 Zirconia-based Dental Posts

The requirement for more esthetic posts, especially under all ceramic restorations, has started the development of new post materials (Fig. 2.10). In situations where all-ceramic restorations are used for restoring anterior teeth, metal posts may result in unfavourable esthetic results, such as a grey discoloration of translucent all-ceramic crowns and the surrounding gingival margin. Additionally, corrosive reactions with prefabricated posts may cause complications involving the surrounding tissues and oral environment, including a metallic taste, oral burning, sensitization, oral pain, and other reactions. These concerns have led to the development of white or translucent posts made of zirconia and other ceramic materials.

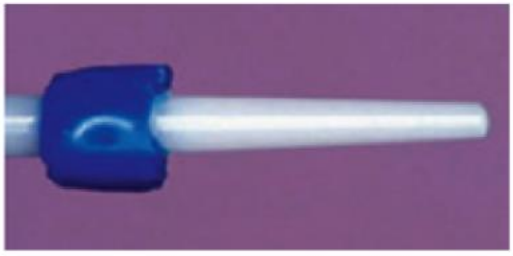

Fig 2.10 - Zirconia-based dental posts

2.1.19.2 Zirconia based crown and bridges

The fabrication of zirconia frameworks of either pre-sintered or highly isostatic pressed zirconia for crown and bridge has also been employed, as shown in Fig. (2.11). Zirconia frameworks offer new perspectives in metal free fixed partial dentures and single tooth reconstructions because of zirconium's high flexural strength of more than 900 MPa and showed good first clinical results.

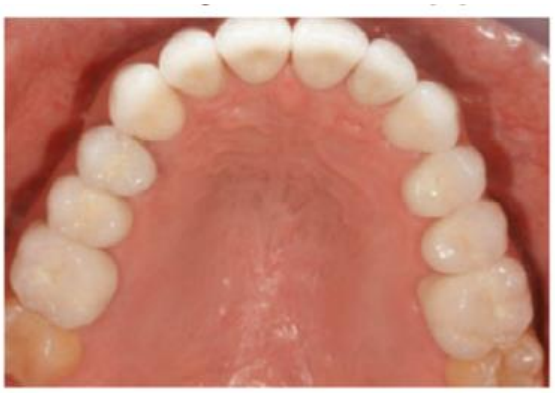

Fig 2.10- zirconia based crown and bridge

2.1.19.3 Zirconia based implant abutment

Utilizing zirconia as implant-supported restorations is due to the higher toughness and the lower modulus of elasticity of zirconia. In stabilized and transformation toughened forms, zirconia provides some advantages over alumina in order to solve the problem of alumina brittleness and the consequent potential failure of implants. These abutments are distinguished by their tooth-matched colour, their good tissue compatibility, and their lower plaque accumulation.

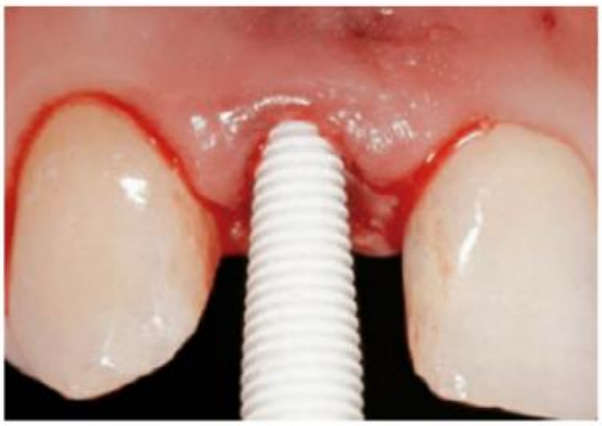

Figure 2.11: zirconia-based implants

2.1.19.4 Zirconia-Based Esthetic Orthodontic Brackets

Besides the dental applications that were mentioned previously, zirconia has also been applied for the fabrication of esthetic orthodontic brackets. Polycrystalline zirconia brackets, which reportedly have the greatest toughness amongst all ceramics, have been offered as an alternative to alumina ceramic brackets. They are cheaper than the monocrystalline alumina ceramic brackets but they are very opaque and can exhibit intrinsic colours making them less aesthetic. Good sliding properties have been reported with both stainless steel and nickel-titanium arch-wires along with reduced plaque adhesion, clinically acceptable bond strengths and bond failure loci at the bracket/adhesive interface [31].

2.1.20 Pain Management

Pain is a primal instinct in humans of an unpleasant sensation and emotional experience associated with existing or potential tissue damage with the sole objective of alerting the body's defence system to react to a response in order to prevent additional tissue damage. Pain is the most common reason for seeking medical help. Pain affects around 20% of all patients worldwide, with 10% of those diagnosed with chronic pain. Approximately 40 percent of patient who are doing treatment for primary pain reports inefficient pain relief and many pain medications have side effects such as hepatotoxicity, depression, respiratory depression and addiction. The recent opioid epidemic, which is the main cause of medication-induced overdosing, emphasises the urgent need for new chronic pain treatment choices. Chronic pain affects 20 percent of the adult population and is linked with the disorders like cancer, diabetes, inflammation and trauma injury or surgery. Patients who are suffering from chronic pain are also at risk for anxiety and depression. For an individual the burden of suffering from the pain not only includes physical and mental distortion but also cost of the medical, reduced social relationship and decreased work productivity. Chronic pain is also financial burden to the government as it affects the productivity of the people and socioeconomic cost of healthcare expense of people. As the population ages, the suffering from people also increases. At the end pain degrades one’s quality of life and one of the main reasons for long term inefficiency. Despite this obvious need, treating pain efficiently and without unfavourable side effects remains a challenge.

Nanomedicine is a fast-emerging discipline, but the intricacy of pain physiology and the persistent nature of chronic pain have limited its application to pain management. Nanotechnology, on the other hand, will play a key part in the future generation of pain management. Nanomaterials can be used as drug carriers that aim for specific cell, tissue or organs as well as devices to identify the chemical source of pain. Nanoparticle drug carriers provide better efficacy with reduced dosages and give longer-term pain relief.

2.1.21 Psychology of pain

To improve pain management, a greater understanding of the physiology of pain is required to minimise dose, create novel medicines that act on specific targets as well as toxicity. Pain is a distressing, multidimensional sensory and emotional experience that combines physical, emotional, and psychosocial aspects and is linked to actual or potential tissue damage. Perception and severity of pain for individual may differ and difficult to treat and investigate as it is subjective. The origin of pain pharmaceutical therapies is based on different mechanism taking account of both physical

and psychological aspects of pain. The pain psychology should be better understood in order to effectively measure pain and produce more effective pain nanocarrier drugs.

2.1.21 Basic mechanism of pain

Primarily pain mechanism goes through three stages a) transduction b) transmission and c) modulation when noxious stimuli is present. In specific nociceptive pathways, stimuli are first converted to chemical tissue, then chemical tissue and synaptic cleft events are transformed into electrical events in the neurons and in the last stage of transduction, at the synapses electrical events are transduced as chemical events. Electrical signals are conveyed along neural pathways in the transmission stage, when neurotransmitters send information from one cell's synaptic terminal to another cell's synaptic terminal. Through primary afferent neuron, DH, and higher rain center up- or down-regulation, modulation occurs at all levels of nociceptive pathways.

2.1.21.1 Neuron

Neurons are regarded to be the essential components in the central nervous system (CNS) and peripheral nervous system (PNS) that carry all nociceptive information via three phases. In our bodies, we have three types of neurons: a) sensory neurons or afferent neurons b) interneurons c) motor neurons or efferent neurons. The soma, axon, and dendrites are the three parts of a neuron. Synapses carry chemical and electrical messages between neurons, forming a complex network in our bodies. One neuron's impulses are received by the dendrites and soma, and then transmitted by the axon throughout the body. This is the reason why small pulses also known as action potentials forms within the neuron, which transmit from the soma, travel along the axons to activate the synapses, and are then sent to other neurons and act as a pathway to continue the signals from its source to either the spinal cord or the brain, where a response is ultimately interpreted to be executed. The sensory neuron, which is found in the dermis and epidermis, responds to stimuli such as touching and sends the signal along, whereas the primary purpose of the motor neuron is to receive signals from the brain and spinal cord, then produce responses such as muscle contractions and influence glandular outputs.

2.1.21.2 Axons

The primary component of neuron is axon or nerve fiber. Axon transmits the signal from dendrites to axonic terminal unilaterally and from one neuron to other. The myelinated axon has myelin sheath also known as node of Ranvier which enhances the propagation speed of the signals. Unmyelinated axon impulse speed is slower than myelinated axon impulse speed. The node of Ranvier contains K^+

and Na^+ channel which reserves energy when the action potential transmits through the neuron. Sensory (afferent) neurons are categorized into three primary groups: group A, B, C according to the velocity of a conducted impulse, axon diameter, and function of an axon. Motor neurons are categorized into Type Ia, Ib, II, III, and IV.

Group A

Group A nerve fibers can be further subdivided into Aα, Aβ, Aγ and Aδ each with its own set of features.

1) Type Aα: It mainly determines the proprioceptive function.

2) Type Aβ: it is a low-threshold, cutaneous, slow or fast adapting type of mechanoreceptors, and is a Type II afferent fiber from the stretch receptor. The Aβ-fibers belong to laminae III and IV.

3) Type Aγ: Type II afferent fibers from the stretch receptors.

4) Type Aδ: it is well-known as the thermal and mechanical nociceptors that terminate in the rexed laminae I and V. It is a Type III afferent fiber.

Group B

These fibers are myelinated. Their conduction velocity ranges between 3-14 m/s. The preganglionic nerve fibers of the autonomous nervous system (ANS) and general visceral afferent fibers are in this group.

Group C

These fibers are unmyelinated. The diameter of these fiber is less than 2 µm and have conduction velocity of 2 µm/s. The nerve fibers at the dorsal roots and postganglionic fibers in the ANS falls in this group. These fibers have nociceptive function. Group C fibers are activated by chemical, thermal and mechanical stimuli [32].

2.1.21.3 Action potential

When the Ca^{2+} enters, it triggers the release of neurotransmitter at the axon end and the signals are then transmitted via different neurons by an action potential. Threshold potential and resting potential of neurons are two potential that allows transmission of signal through neurons. The resting and threshold potential are approximately −70 and −55 mV, respectively. Na^+ stored outside the cell is more than K^+ inside the cell as a result the potentials are negatively charged. When different channels are activated then these ions pass through lipid bilayer of the neurons. The action potential of the neuron is shown in the figure.

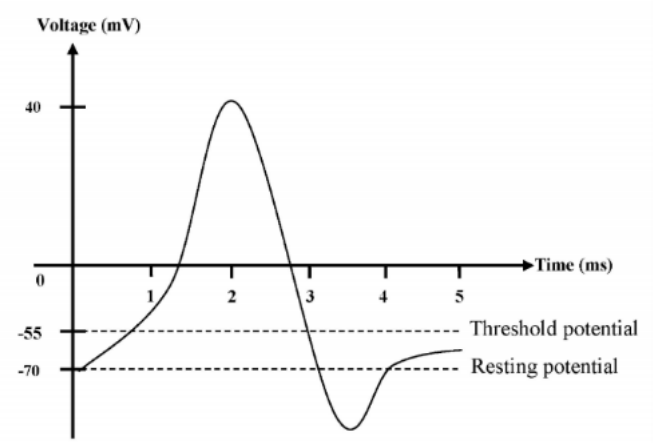

Figure 2.12 Action potential

2.1.21.4 Synaptic transmission

This transmission known as chemical events that transmit the impulse among neurons. The chemical synapse occurs in the synaptic cleft. The gap between the presynaptic and postsynaptic membranes is known as the synaptic cleft. When action potential opens Na_v channels, the Na^+ enters and activates VOCC which in turn allows Ca^+ to enter the axon terminal. The calcium ions are then bind with the protein and interact with soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins. The SNARE protein causes the release of contents like neurotransmitter and Ca^{2+} from the presynaptic terminal into the synaptic clefts. These neurotransmitters then bind to the ion channels that are located in the postsynaptic neurons and passes the action potential to the second neuron. In this way, the impulse signal travels from one neuron to the next.

2.1.22 Pain Pathways

Central nervous system and peripheral nervous system both are involved in pain pathways. Pain is felt when the pain receptor that is nociceptor is activated by different stimuli like thermal, mechanical and chemical. The nociceptors are situated on sensory neurons called A and C types of primary afferent fibres. Aδ-type fibres are large, myelinated fibres that transmit acute, well-localized pain quickly; C-type fibres, on the other hand, are small, unmyelinated neurons that transmit sluggish, dull, poorly-localized pain. Noxious stimuli which are tissue damaging stimuli trigger epithelial cell, immunological cell and cell within the circulatory system which release chemical that excite G protein couple receptor, ionotropic receptors, and tyrosine kinase receptors on the peripheral terminals of primary spinal afferent neurons. Lipids, peptides, neurotrophins are among the secreted stimulatory compound by these. When the nerve terminal release neuropeptide like

substance P and calcitonin gene related protein (CGRP), they reactivate receptors on epithelial cells and immune cell then neurogenic inflammation develops. Receptor activation and main sensory neuron channels elicit central transmission of substance P, action potentials, and subsequent glutamate release within the dorsal horn of the spinal cord. Receptor activation triggers transmission of action potential and release of glutamate, substance P, CGRP in the spinal cord. Second-order neurons in the dorsal horn of the spinal cord respond to these signals by activating receptors. When these signals are conveyed to the cortex via the spinothalamic tract, pain is perceived.

2.1.23 Central and Peripheral sensitization

Pain pathways may be changed structurally and functionally like potentiation at the synapses increases and neuronal hypersensitivity resists further harm following injury or damage. Hyperalgesia (heightened sensitivity to pain) is caused by increased sensitivity to noxious stimuli, which can occur after surgery or opioid use. Non noxious stimuli like inclusive of mild contact or warm temperature can also bring out pain which occurs due to other disease or surgery. When an injury occurs, N-methyl-D-aspartate (NMDA) receptors gets activated because of increase in Ca^{2+} ion leading to hypersensitivity. The upregulation of a-amino 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is caused by calcium ion flow. Increased AMPA receptors boost excitation of post synapses and actuate protein kinases including calmodulin dependent protein kinase II. Calcium influx also increases the activity of calcium-dependent kinases like COXs and nitric oxide synthases. This induces neurotransmitter release and activation of downstream second messenger signalling via the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathways, resulting in the synthesis of prostaglandin E2 and nitric oxide.

Sensitization (heightened sensitivity to stimuli) at the peripheral and central levels is important in chronic pain. Nociceptive neurons in the central nervous system activate at sub-thresholds, resulting in neuronal hyperexcitability, which causes central sensitization. Glutamate and neuropeptides are released by activated neurons in the dorsal horn of the spinal cord, which bind to receptors and cause action potentials to fire. In the spinal cord, microglia and astrocytes release cytokines and chemokines that increase neuronal firing. Hyperexcitability at primary afferent neurons causes peripheral sensitization. Ion channels such as transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid type 1 (TRPV1), as well as sodium channels like Nav1.7, Nav1.8, and Nav1.9, govern the activation of peripheral receptors.

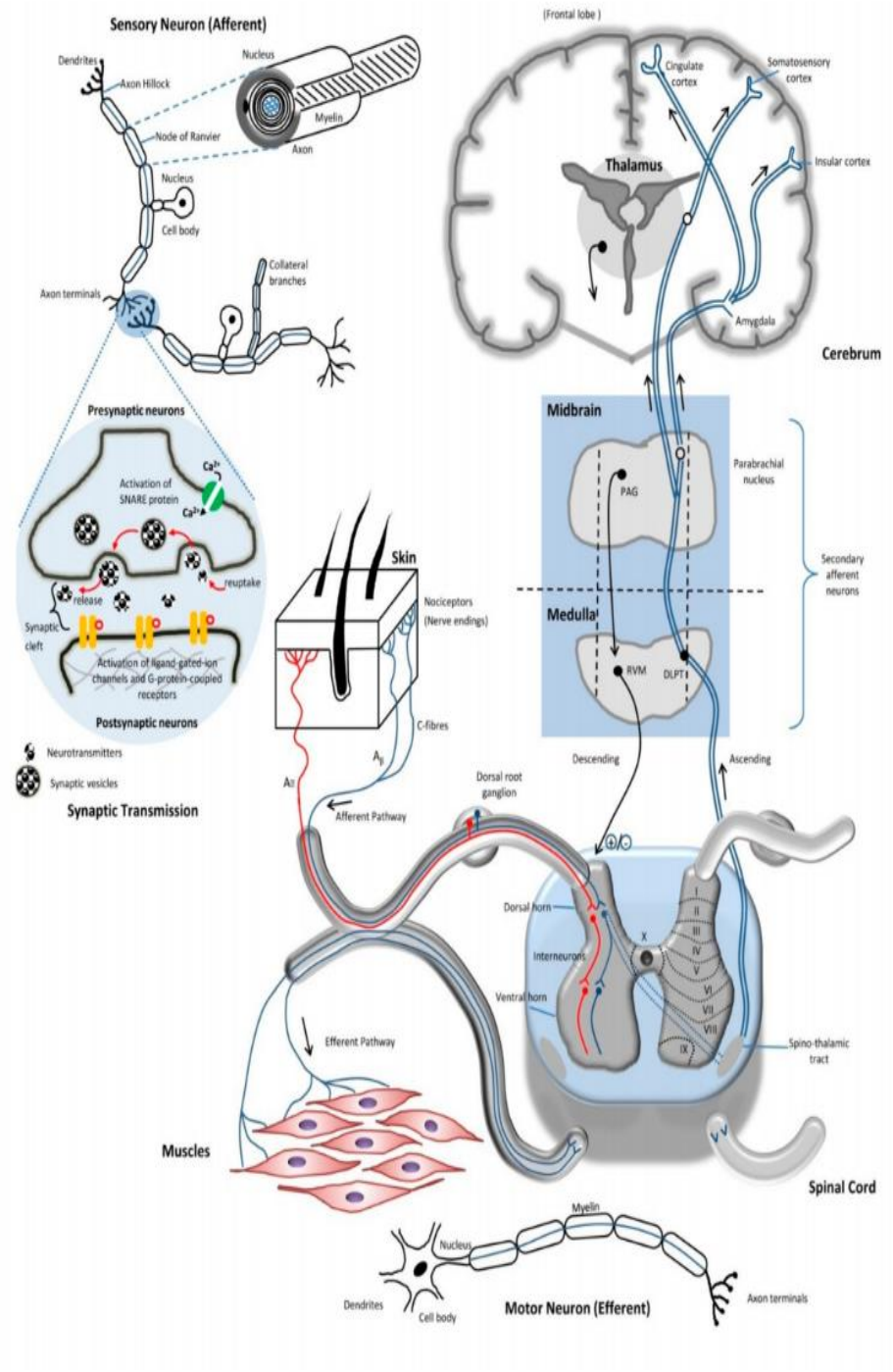

Figure 2.13 The basic route of pain transmission upon noxious stimuli in ascending and descending order, and the illustration of synaptic transmission in synaptic cleft.

2.1.24 Pain and inflammation

Inflammation and pain are inextricably linked. When the vascularized tissue gets damaged, it sends inflammatory responses leading to release of inflammatory mediators like ATP, substance P etc. by T cells, neutrophils, mast cells which causes vasodilation. These pro-inflammatory chemicals also activate pain receptors, boosting calcium and sodium ion influx into neurons and causing action potentials to fire. Injury by-products such as prostaglandins, bradykinin, and histamines encourage pain neurons to produce more inflammatory neuropeptides and cytokines, which worsen inflammation. To maintain the response of inflammation. To maintain the inflammatory response, proinflammatory chemokines (CCL2, CXCL5) and cytokines such as tumour necrosis factor (TNF) and interleukin 1 (IL-1) bind receptors and ion channels. Phospholipids are released by damaged cells and converted to prostaglandin H2 (PGH2) by COXs. PGH2 is converted to PGE2, prostacyclin (PGI2), and PGF2, which mediate fever, increased pain, and inflammation, or to thromboxane A2 (TXA2), which mediates platelet aggregation, via prostaglandin synthases. Inflammation usually subsides once damaged tissues have healed, but it can also become chronic, lasting months or years after the healing period has concluded.

Phospholipase A2 is released after an inflammatory response, and it converts arachidonic acid. Arachidonic acid is converted into prostaglandins through the COX enzymatic pathway, which contains COX-1 and COX-2 (PGs). In platelets, gastrointestinal mucosal cells, and renal tubule cells, COX-1 normally produces thromboxane and PGs. COX-2 is activated at areas of inflammation and creates PGs, which cause pain and inflammation.COX-2 inhibition lowers PG synthesis, resulting in anti-inflammatory and analgesic effects.

2.1.25 Types of pain

a) Acute pain:

Acute pain is the pain that persists for a short amount of time, usually between minutes and 3 months. Acute pain is frequently connected with a soft-tissue injury or a brief sickness, and it normally disappears once the damage or illness has healed Acute pain can become chronic if an injury does not heal adequately or if the pain signals fail.

b) Chronic pain:

The duration of chronic pain is prolonged. It might be continuous or sporadic. Even if the pain isn't always there, headaches can be considered as chronic pain if they persist for months or years.

Chronic pain is frequently caused by a medical disease such as arthritis, fibromyalgia, or a spine problem.

c) Neuropathic pain:

Damage to the nerves or other components of the nervous system causes neuropathic pain. It is often described as shooting, stabbing, or burning pain, or it feels like pins and needles. It can also affect touch sensitivity, making hot and cold sensations more difficult to perceive. Neuropathic pain is a common type of chronic pain. It may be intermittent (meaning it comes and goes), and it can be so severe that it makes performing everyday tasks difficult. Because pain can obstruct normal movement, it can cause to mobility problems. Allodynia is usually connected with neuropathic pain, which is thought to be caused by a nerve injury or dysfunction. Allodynia is a pain sensitization that happens when receptors are exposed to non-painful stimuli repeatedly. Because neuropathic pain does not play a part in our bodies' defence mechanisms and might develop as a persistent sensation, it is referred to as "pathologic" pain. This type of pain can be caused by metabolic sickness or inflammation, such as tumours, trauma, diabetes, infection, or neurological disease. The importance of central sensitization in this approach cannot be overstated. Nerve injury can result in neuropathic pain and have an impact on the somatosensory nervous system. When an axon is damaged, the neurochemistry of the axon can be altered by compression, stretching, and hyperexcitation of the damaged location.

d) Nociceptive pain:

Damage to human tissue causes nociceptive pain, which is a type of pain. It's commonly described as a sharp, achy, or throbbing pain. An external injury is frequently the cause. If one bang his elbow, stub his toe, twist his ankle, or tumble and scrape up his knee, he may suffer nociceptive pain. This type of discomfort frequently affects joints, muscles, skin, tendons, and bones. It might be acute or chronic in nature. Nociception is the name for our nervous system's reaction to damaging stimuli. Nociceptors are nerve endings that are triggered by real or potentially harmful stimuli. The early phases of pain perception are controlled by these nociceptors. The main afferent nociceptors that respond to unpleasant stimuli are the A and C fibres. These nociceptors nerve terminals can be located all over our bodies. A- and C-fibers are found on the skin, but C fibres are found in muscles and joints. A-fibers are excited by heat or mechanical stimuli, leading to prickling, brief duration pain sensation. The C-fibers are excited by Thermal, mechanical, and chemical stimuli. The

receptors in primary afferent neurons have three major functions: excitatory, sensitising, and inhibitory responses. When receptors are stimulated and pain reaches a certain threshold, impulses travel through afferent fibres to the DH (PNS) and medulla (cranial). Silent nociceptors are extra nociceptor fibres found within the viscera that lack a terminal and are only sensitised by chemical mediators generated during inflammatory reactions.

e) Inflammatory pain:

When body tissues are harmed, a natural biological process known as inflammation takes place, in which damaged cells are eliminated and tissues begin to heal. Neutrophils, which go to the site of injury via the circulation, are the first responders to an inflammatory reaction, followed by the release of additional chemical mediators. Hyperalgesia, allodynia, and sympathetic sustained pain are frequent inflammatory reactions. Inflammation can also cause mast cells to degranulate, which releases platelet activating factor (PAF), which increases the production of 5-HT from circulating platelets. When inflammation occurs, blood flow to the area rises, causing redness and swelling as a result of pain generated by primary afferent neuron activation and sensitization. The free radicals are then released as a result of the localised inflammatory reaction. The free arachidonic acid (AA) is subsequently released from the phospholipids and transformed into prostaglandins (PG) via the cyclooxygenase (COX) pathways by the localised inflammatory response.

f) Radicular pain:

Radicular pain is a type of pain caused by the crushing or irritation of a spinal nerve. By way of the spine and spinal nerve root, it radiates from the back and hip into the leg(s). Tingling, numbness, and muscle weakness are common symptoms of radicular pain. Radiculopathy is pain that radiates from the back into the leg. The pain is commonly referred to as sciatica since it is caused by a problem with the sciatic nerve. This form of pain is usually constant, and it can be felt deep in the leg. Walking, sitting, and a variety of other activities might aggravate sciatica. Sciatica is one of the most common types of radicular pain [33].

2.1.26 Current pain treatment

2.1.26.1 Non-opioid Drugs

Non-opioid analgesics like acetaminophen (Tylenol), non-steroidal anti-inflammatory medicines (NSAIDs), and adjuvant therapies are commonly used to treat chronic pain (e.g., antidepressants, anticonvulsants, and corticosteroids). Acetaminophen is a first line treatment for mild musculoskeletal pain (e.g., osteoarthritis, lower back pain). Acetaminophen inhibits oxidised cyclooxygenases (COX) from producing proinflammatory prostaglandins, providing analgesic and antipyretic (fever-reducing) actions.

The most frequent first-line therapies for inflammation-related pain are NSAIDs including aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve). NSAIDs, unlike acetaminophen, treat both pain and inflammation. Many nonsteroidal anti-inflammatory drugs (NSAIDs) are COX inhibitors, which lower prostaglandin production and hence lessen inflammation.

NSAIDs are a class of analgesics that can alleviate pain and reduce inflammation at the site of injury. NSAIDs are enzyme inhibitors that target cyclooxygenases which are responsible for the production of prostanoids (e.g., thromboxane (TXA2), prostacyclin (PGI2), and prostaglandins). Prostaglandins are inflammatory mediators that regulate inflammation, control blood pressure, and are involved in the contraction and relaxation of both smooth muscle and blood vessels, while thromboxane causes platelet aggregation and is important for thrombosis.PGE2 is the most important prostaglandin for pain modulation, and it generates inflammatory pain by binding to its receptors (EP1–EP4, particularly EP4) and activating protein kinase A (PKA) and tetrodotoxin (TTX)-resistant sodium channels (e.g., Nav1.8). PGE2 also aids the shift from acute to chronic pain by activating the epsilon isoform of protein kinase C (PKCε).

Adjuvant analgesics like antidepressants and anticonvulsants are progressively being utilized to treat neuropathic and nociplastic pain. Antidepressants are not acute analgesics, although they can help with chronic pain. Tricyclic antidepressants (TCAs) like amitriptyline, serotonin-norepinephrine inhibitors (SNRIs) like duloxetine, and selective serotonin reuptake inhibitors (SSRIs) like paroxetine are among the antidepressants used to treat neuropathic pain. TCAs decrease norepinephrine and serotonin presynaptic reuptake of norepinephrine and serotonin and restrict 2 adrenergic, H1-histaminergic, and muscarinic cholinergic receptors, and are beneficial in 33–50 percent of chronic pain sufferers. SNRIs are noradrenaline and serotonin reuptake inhibitors that act in 20–25 percent of patients, depending on the dosage and concentration of the medicine. Duloxetine is useful in the treatment of diabetic peripheral neuropathic pain because it has a high affinity for norepinephrine and serotonin reuptake transporters. SSRIs, which block serotonin reuptake, help pain in only 14 percent of patients.

Local anaesthetics and steroids are two more non-opioid pain therapies. LAs are commonly used to provide immediate pain relief or to cause numbness. They're frequently given before surgery to decrease any pain feelings at the surgical site, particularly in dental surgery. The main mechanism of action of LAs is the blockage of voltage-gated sodium channels in neurons (Nav). LAs bind to the pore area of ion channels (Nav1.1–Nav1.9) and prevent Na+ from entering the neuron, preventing action potential firing and nerve conduction blockage. Short-acting pain management is usually achieved with local anaesthetics such as lidocaine. Lidocaine blocks voltage-dependent sodium channels, which modulate pain transmission, and hence lessens intense burning pain like postherpetic neuralgia in shingles. Lidocaine is a local anaesthetic that can be administered topically

to treat pain or carefully injected as a nerve block to relieve pain and discomfort following medical operations. Capsaicin is a nociceptors-targeting topical cream that is a highly selective agonist of noxious heat-sensing TRPV1.

2.1.26.2 Opioid drugs

Opioids are one of the most useful medicine for pain but their action mechanism also have high risk. Opioids like morphine

When nociceptive symptoms become more severe and non-opioid analgesic regimens are insufficient, opioids are utilised. Opioids are powerful analgesics that have long been regarded as the most effective non-neuropathic pain relievers. Opioid drugs engage opioid receptors across the peripheral and central nervous systems, acting similarly to endogenous opioids. When opioid receptors on the presynaptic terminal are activated, the beta-gamma subunit blocks voltage-gated calcium channels, blocking the release of glutamate and the neuropeptides substance P and CGRP.

For pain management, many opioid medications stimulate the opioid receptors. Morphine is a natural opiate that is used to alleviate pain ranging from mild to severe. Fentanyl, hydrocodone, methadone, and oxycodone are synthetic opioids that are similar to endogenous opioid peptides but have a higher strength. Because it antagonises NMDA receptors and functions as a serotonin-norepinephrine inhibitor, methadone is used to treat both nociceptive and neuropathic pain [34].

2.1.27 Trace metals

Trace metals are inorganic micronutrients that are present in very low concentrations in body fluids and tissues. Their dietary requirements are in µg to mg/day. They are required for the proper functioning of many enzymes and other proteins. Their deficiency can lead to specific signs and symptoms. Sometimes the deficiency is not dietary but due to transport or recycling defects. In humans, metals are obtained exogenously and require intestinal absorption and transport to the appropriate intracellular compartment for function.

2.1.27.1 Zinc

Zinc is second to iron as the most abundant trace metal. It is ubiquitous, found in all tissue types and fluids, as well as being the most abundant intracellular trace element. It is an important metal cofactor, essential for the functioning of over 300 enzymes that are involved in major metabolic pathways. In addition, it participates and regulates nucleic acid and protein synthesis, and is required for the functioning of at least 3000 transcription factors. A summary of zinc metabolism is given in Fig. 2.14. Elevated zinc levels are generally of little clinical consequence, although zinc and copper levels tend to be inversely related and hence high zinc levels can result in low copper levels and vice versa. Copper, on the other hand, plays a critical role in physiologic redox chemistry4 and both deficiency and excess have pathogenic consequences. Both copper and zinc affect cellular iron levels as well. Copper will be discussed in a following section. Zinc performs many roles in the physiology of the human body including catalytic, regulatory, and structural roles. Since Zn is required for anabolic processes, zinc deficiency has a significant effect on growth, tissue integrity, and wound healing. In plasma, zinc is bound to albumin and α-2-macroglobulin. Although there is no dedicated zinc store in the body, about 10% of intracellular zinc in the liver as well as some other tissues is available as a functional pool that exchanges with the plasma pool, and is important in maintaining the plasma concentration that undergoes a rapid turnover.

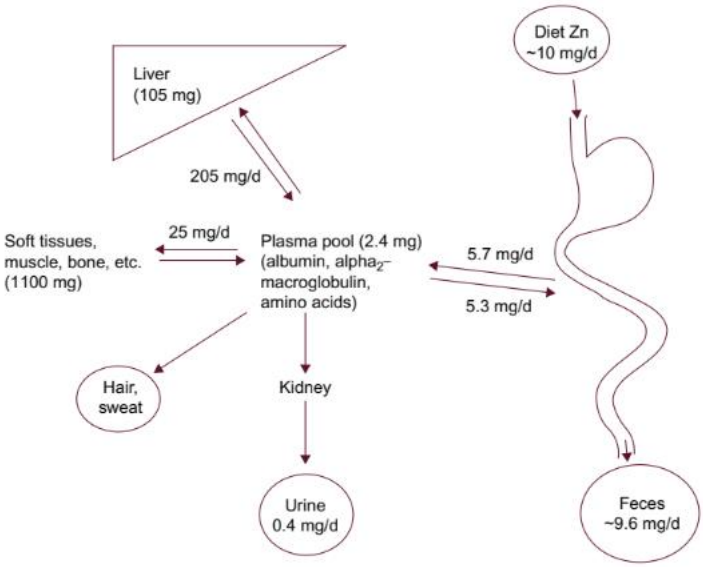

Figure 2.14 summary of zinc metabolism

2.1.27.1 Copper

As with zinc, copper is also an essential metal required for growth and development. It is associated with a number of metalloproteins and is required by all tissues for proper cellular metabolic function. Control of its levels is critical to avoid deficiency or excess, both of which are detrimental. Copper can adopt both an oxidized (Cu2+) and reduced (Cu+) configuration and hence, is a catalytic cofactor in oxidation–reduction reactions and is vital for proper functioning of enzymatic pathways involved in energy production and antioxidant activity. The median copper intake in the United States is approximately 1.0–1.6mg/day. The majority of dietary copper absorption takes place in the duodenum via the high affinity transporter, hCTR1 (human copper transport protein 1), in the basolateral membrane of the intestinal epithelial cell. Transport is regulated by the intracellular C-terminal domains of the homotrimer while actual transport is mediated by the extracellular and transmembrane domains. It is postulated that CTR1 is needed for the release of dietary copper from subapical vesicles for delivery to copper chaperone proteins, mitochondrial cytochrome C oxidase, and Cu-ATPases. Reductases in the apical membrane are necessary for the reduction of Cu2+ to Cu+, the ion that is recognized by the transporter. Divalent metal transporter I and endocytic/ pinocytic processes are postulated to be involved in the transport across the apical membrane. A low-affinity transporter, CTR2, has also been identified, the exact function of which, has not been elucidated but likely facilitates movement of copper across the apical (luminal) membrane. Cu-ATPase ATP7A is then responsible for the transport of copper into intracellular vesicles and

secretion of copper across the basolateral membrane into the bloodstream. Copper is then transported in the blood bound to albumin, ceruloplasmin, transcuprein, and low molecular weight copper–histidine complexes for delivery to tissues. It is readily taken up by hepatocytes via hCTR1. After uptake, it is stored via chelation by metallothionein, is bound to chaperone proteins for intracellular trafficking to copper-requiring enzymes or is bound to reduce glutathione. ATP7B is necessary for the efflux of excess copper, particularly in the liver. It is also postulated to result in copper sequestration and storage in other tissues, such as in the kidney and intestine. Both ATP7A and ATP7B are localized perinuclearly and thought to be targeted to the trans-Golgi network under basal conditions. They both receive copper, which binds to an N-terminal metal binding site, from a chaperone protein, Atox1. Precise control of copper homeostasis is necessary and disruption thereof results in disease. Two pools of circulating copper exist. The first pool is copper that is tightly bound to ceruloplasmin, which includes about 85–90% of circulating copper and is thus not freely available to cells and tissues. The remaining 10–15% of circulating copper is less tightly bound to albumin and other small molecules in the blood and is more freely available to cells [35].

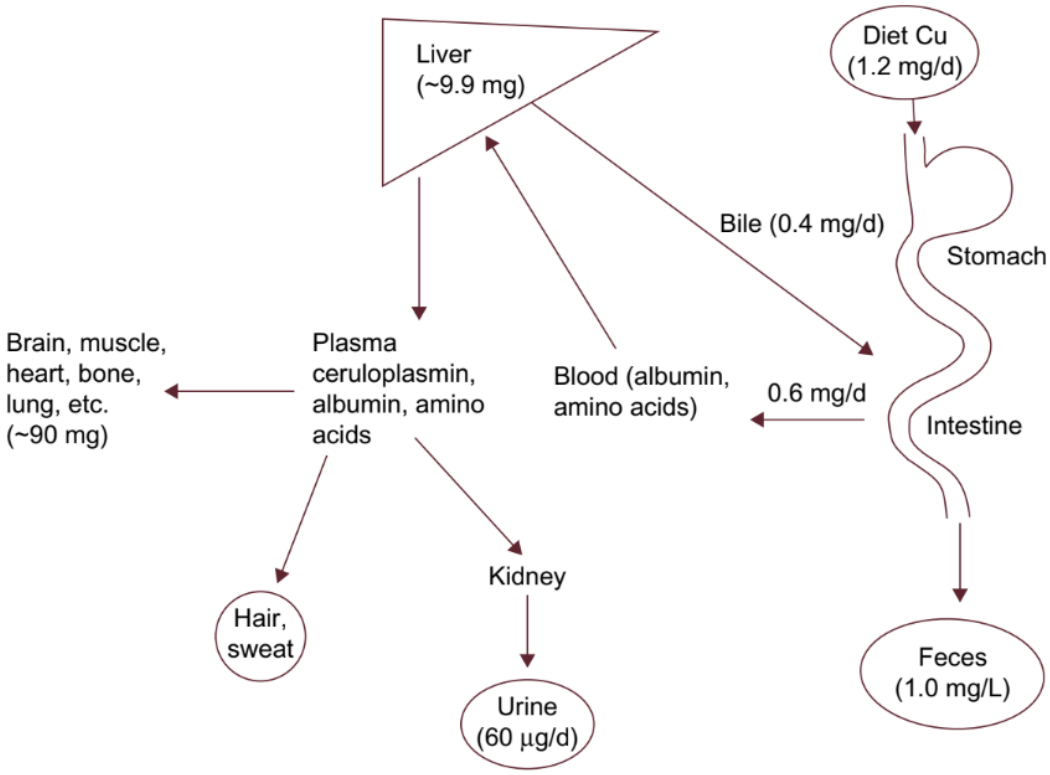

Figure 2.15 Copper metabolism process

2.1.27.3 Manganese

Manganese (Mn) is necessary for healthy connective tissue and bone development. As with other trace metals, Mn is required for metabolic function as it acts as a cofactor for a number of enzymes including Mn-specific glycosyltransferases, superoxide dismutase, pyruvate carboxylase, arginase, and phosphoenolpyruvate carboxykinase. Approximate daily requirement for Mn of 1–6mg is readily supplied by a normal diet. Mn deficiency has not been definitively documented in humans although deficiency in other animals, particularly cattle, results in ataxia and skeletal abnormalities. Prolidase deficiency that leads to skin ulceration, mental retardation, increased urinary excretion of iminopeptides, and recurrent infections has been associated with Mn deficiency. Ingestion rarely leads to toxicity as intake via enterocytes and excretion by biliary duct cells is tightly regulated. Excess Mn, however, is quite toxic and usually results from occupational inhalation exposure, although cases of hyper-manganesemia have been reported with ingestion of contaminated drinking water. Toxicity results in biphasic physical decline with initial psychiatric symptoms followed by a progressive dystonic gait, akinetic rigidity, and bradykinesia. The majority of experimental work elucidating the effects of Mn has been focused on genes associated with the development of Parkinson's disease because of the link between Mn toxicity and dopaminergic neurodegeneration. Recently, mutations in SLC30A10, which encodes a Mn transporter, have been identified resulting in autosomal recessive dystonia with brain Mn accumulation, polycythaemia, and hepatic cirrhosis.

2.1.27.4 Selenium

Although dietary selenium deficiency and toxicity have been recognized in the past, only recently have inborn errors of selenium metabolism been elucidated. Like many other essential elements, selenium is involved in multiple pathways through more than 30 biologically active selenocysteine-containing proteins. Selenium enters the body through food mainly as selenomethionine from plants. Average daily intake in the United States ranges from 80 to 220µg. The reference range for plasma selenium is about 60–150 ng/mL. Selenium deficiency (serum concentration <40ng/mL) is rare and is associated with loss of glutathione peroxidase activity. Dietary selenium deficiency is generally seen in hospitalized patients or with the use of TPN. Selenium deficiency tends to be associated with either cardiomyopathy or symptoms of hypothyroidism, whereas excess causes hair loss, nail abnormalities, dermatitis, nausea, diarrhoea, fatigue, peripheral neuropathy, and an unusual garlic breath odour. Toxic levels have not yet been well defined. Selenoproteins are unique in that they contain the amino acid selenocysteine. To generate these proteins, UGA triplets, which are usually stop codons, must be recoded and recognize a specific serine/selenocysteine tRNA. In this process, serine is charged onto this tRNA by Ser-tRNA synthase and then converted to selenocysteine-by-selenocysteine synthase (SEPSECS). A specific elongation factor (EF-Sec) is also required to carry

this tRNA to the ribosome, which upon interacting with translation factors allows for the insertion of selenocysteine into the protein rather than resulting in translation termination. To date, 25 genes encoding selenoproteins are known, all of which catalyse oxidation-reduction reactions. Regulation of bio synthesis of selenoproteins depends upon selenium availability, mRNA levels, and translational control mechanisms. Inflammation and chronic illness as well as statin and aminoglycoside use may lead to decreased levels of selenoproteins, but little data is available, particularly for infants and children.

2.1.27.5 Iron

Iron is the most abundant essential trace element in the human body. The total content of iron in the body is about 3–5 g with most of it in the blood and the rest in the liver, bone marrow, and muscles in the form of heme. Iron is absorbed in the gut from diet in case of depletion and transported in the form of ferritin. Hemosiderin is a golden-brown pigment which is a by-product of metabolism of ferritin and is deposited in the cells of the reticuloendothelial system. Homeostasis of iron maintains the iron levels in serum within normal range only by upregulation or downregulation of absorption mechanism of iron which is unique because it maintains homeostasis by regulating the absorption and never excretion.

Biological function of iron:

Heme is the major iron containing substance in ferrous or ferric state which is present in haemoglobin, myoglobin, and cytochrome. There are numerous enzymes associated with iron, namely, cytochrome a-c, p450, cytochrome c reductase, catalases, peroxidases, xanthine oxidases, tryptophan pyrrolase, succinate dehydrogenase, glucose-6-phosphate dehydrogenase, and choline dehydrogenase. Heme forms covalent bonds with the globin protein to form haemoglobin which is the major oxygen carrying pigment in RBCs of mammalians. It takes part in a myriad of metabolic cycles such as in the energy producing reactions (the cytochromes of the Krebs cycle) in all the cells and activates the energy producing oxidizing enzymes. Apart from participation in maintaining innumerable physiological and metabolic processes, it is also necessary for DNA, RNA, collagen, antibody synthesis, and so forth.

2.1.28 Advancement in materials in Ophthalmology

Eye implants are used to restore functionality of cornea, lens, vitreous humor etc. when they are damaged or diseased. Ophthalmology is a field that has rapidly advanced as a result of the development of new techniques and materials. Biomaterials are an important component of the procedures that are used to improve and maintain vision. In this section we will review the materials that make up normal structures of the eye, as well as, those used for replacements. These biomaterials include viscoelastic solutions, intraocular lenses, contact lenses, eye shields, artificial tears, vitreous replacements, correction of corneal curvature and scleral buckling materials.

2.1.28.1 Anatomy of eye

The eyeball is approximately spherical and has a diameter of about 2.5 cm. It contains three layers including the fibrous outer coat, vascular middle coat and light sensitive inner coat. The outer fibrous coat consists of the sclera (white portion) which is continuous with cornea (transparent portion). In the back of the eye is a vascularized thin pigmented membrane, the choroid that supports the retina. The retina is a light sensitive membrane lining the internal surface that transudes light intensity and colour into electrical signals. Light passes through the cornea, the anterior and posterior chambers, aqueous humor, the lens, and the vitreous body and then impinges on the pigmented cells of the retina and thereby stimulates photoreceptor cells, the rods and cones. Rods are sensitive to dull light and give vision of movement and shape. Cones are sensitive to bright light and are receptors of colour and shape outline. Photo stimulation of these cells results in the production of nerve impulses that are conducted to brain via optic nerve. The aqueous humor fills the anterior chamber and the vitreous humor fills the posterior chamber of the eye carrying nutrients to the avascular cornea and lens. Continuous production and drainage of the fluid maintain an intraocular pressure of about 24-mmHg. Lens is a transparent structure between the anterior chamber and vitreous humor that is stretched into an oval shape by suspensory ligaments. Eye structures including the cornea, sclera, lens and vitreous body are composed of collagenous tissue that contains other macromolecules such as glycosaminoglycans and the crystalline proteins of the lens termed crystalline. Although many eyes tissue contain type I collagen, posttranslational modification of type I collagen varies between different tissues of the eye. The vitreous body, a gel like material, occupies about 80% of the eye. The vitreous body is mostly water containing thin diameter type II collagen fibrils surrounded by a matrix of hyaluronic acid and other materials.

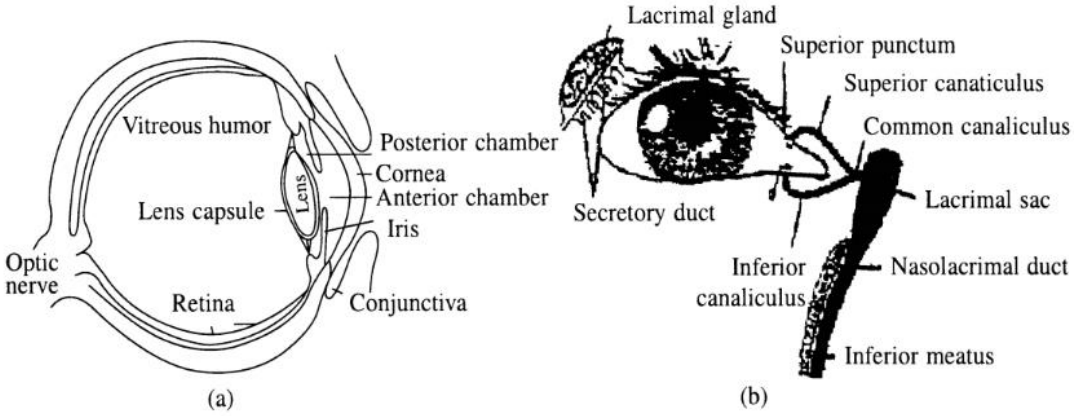

Figure 2.16 (a) Anatomy of the eye and (b) The lachrymal drainage apparatus.

Out of all the sense organs eye is considered as the most important and sensitive sense organ. It is not only sensitive but also equally complex system. Eye is a soft organ and most of the part is a vascular. It is housed in an eye socket, orbit. Light travels through the eye by crossing various layers, the outer most is tear layer and subsequent layers in order of appearance are corneal, aqueous humor, lens, vitreous humor, and retina. Finally, image is formed at retina and it is sensed through lens optics which is connected to the brain through macular part. Any obstruction in any of the layer leads to blurred vision or blindness. The transplantation of the part is reported, but the supply is less than the demand. Therefore, there is great need of artificial support for the systems.

2.1.28.2 Contact lens

Contact lenses are used to correct refractive error in eye. Therapeutic contact lenses are being used nowadays to deliver drug to treat various ocular diseases. Leonardo da Vinci et al. is the person who has invented the use of contact lenses for the first time in 1508. There are two types of lenses, hard contact lens and soft contact lens. Initially they were made up of glass taking moulds of rabbit or cadaver eyes. The discovery of polymethyl methacrylate (PMMA) led to the idea of usage of polymers for the development of contact lenses. However, PMMA lenses are hard and are difficult to wear for longer durations as these lenses do not permeate oxygen to pass through them. Wearing PMMA lenses obstructed oxygen diffusion hence there is a need for other alternative material. To address this an attempt was made in the form of rigid gas permeable contact lenses which are made by copolymerising methyl methacrylate (MMA) with trimethyl siloxy silane (TRIS) which have been licensed to extended wear up to 7 days. In subsequent years, the synthesis of poly hydroxyl ethyl methacrylate (PHEMA) led to the manufacturing of soft contact lenses in 1961. PHEMA gives excellent comfort and is having greater elastic modulus, higher water content up to 38% of water. In addition to this various hydrogel-based lenses were also made from polymers like N-vinyl

pyrrolidinone and glyceryl methacrylate. Although these lenses were comfortable to wear the main drawback is that these hydrogel- based lenses must be very thin and permeable of oxygen, but reduction in thickness led to loss in strength. Another type of soft contact lenses was made up of polydimethylsiloxane (PDMS), it is having higher oxygen permeability. But the problem with PDMS is its low surface energy results in poor wetting. Research is being carried out to increase the wet ability of the lens by grafting with hydrophilic polymers. Till date, PHEMA is most commonly used in contact lens with up to 90% water content for extended use.

2.1.28.3 Intra ocular lens

Cataract is one of the most dreadful diseases that lead to blindness by clouding of the lens. The removal of natural lens leads to withdrawal of cloudiness. Later, to reinstate the natural vision, an intra ocular lens (IOL) is placed. Typically, IOL have two parts: optic and haptic. Haptic may be made up of same material or different material. PMMA is the widely used material for manufacturing of IOL. It is selected because of its high biocompatibility and less weight. Though PMMA has been used for 40 years it has its own disadvantages like less surface energy results to damage of corneal endothelium. Polymeric coatings of NVP and HEMA are being coated to improve the bio-compatibility and to increase the surface energy. In addition to PHEMA hydrogels, collagen fibers and acrylic polymers are used for manufacture of foldable IOL. Recently, thermo sensitive polymer, poloxamer hydrogel has been studied for IOL and the pilot study showed satisfactory results.

2.1.28.4 Corneal implant

In order to alter the refractive state of the eye permanent implants are inserted into cornea. Previously the implant completely replaces the entire thickness of cornea but recent advancements are available where only selected layers can be replaced. Initially corneal implants were made from flint glass later they were replaced by PMMA. Though PMMA is a good polymer, it obstructs nutrition transport in the cornea and there are reports of mechanical irritation and thinning of epithelial layer above the cornea. Later, polysulfones were selected for making thin and high refractive index film to replace natural cornea, but polysulfones is impermeable to aqueous solutions and results in poor nutrient transport. So, the surfaces are made porous with a pore size of 10µm. In order to improve the design, hydrogel based corneal implants came into picture, but they were unable to match the refractive index of natural cornea. To improve the mechanical feature and bio adhesion of the artificial cornea, the design has further improved by using core-skirt approach. The material which has been studied in the design is Poly vinyl alcohol, PHEMA, graphite. Other hydrogel systems are also tried like bacterial cellulose, but clinical trials are required to prove the efficacy. Myopia can also be corrected by altering the surface area of the cornea. A specialized ring is surgically inserted into the corneal surface to flatten the surface and adjusting the focal point on to fovia. PMMA rings

are approved by FDA in 2004 for treatment of keratoconus. These are also exempted under humanitarian device exemption.

2.1.28.5 Scleral buckle

Retinal detachment is a severe condition where retina gets peeled off from its basement membrane. Scleral buckle pushes the sclera and brings chroid back in contact with retina. A wide variety of materials are used for the formulation of scleral buckles, in early days tendons of the same patient were used; though they eliminate out foreign body reactions but it required double surgery. The elasticity of implants is the major drawback as the exact required dimensions of the buckle cannot be achieved. Many other biodegradable materials are being used but the most accepted and widely used substance is gelatin derived from porcine skin. The main problem with the absorbable buckles is inefficient buckling effect. Therefore, non-absorbable buckles came into picture which is made up of soft silicones and silicone sponges. The buckles are soft even after implantation thereby preventing the erosion of underlying sclera. In addition to soft silicones various materials like poly glyceryl methacrylate (PGMA), poly hydroxyl ethyl acrylate (PHEA), and methyl acrylate hydroxy ethyl acrylate (MAI). Out of the three, MAI possess better bulk properties while PHEA breaks on swelling and PGMA has poor tensile strength [37].

2.1.29 Advancement of materials in Otology

Scaffolds are routinely used in the middle ear to provide support after tympanic membrane and ossicular chain reconstruction, to allow middle ear aeration, middle/external ear packing, to provide haemostasis or to promote tissue regeneration. The perfect scaffold material for middle ear packing has been described as being biocompatible; causing minimal inflammation, adhesion and foreign body reaction, no osteogenic, nonallergenic, nonototoxic, absorbable, malleable and chemically and structurally stable. Silastic is the most common silicone used in otology as a middle ear spacer, for endolymphatic sac decompressions, cochlear implant manufacturing, and it has been recently studied as a frame for auricular reconstruction. It has also been used in the surgical treatment of auricular hematomas by accommodating Silastic sheets on the auricular surface offering easy suture placing and wound monitoring. Other non- absorbable materials used in otologic surgery are Teflon, polyethylene and titanium. Absorbable scaffolds Gelatin-based materials Gelfoam is derived from purified porcine skin, completely made of collagen. This material is porous, highly absorbent, no soluble in water and non-elastic. Commercially, Gelfoam comes in a sterile pack, and is around 4 mm thick with variable pore size (30-700 μm). It is the most commonly used absorbable gelatin sponge. Hyaluronic acid is a high-molecular weight polysaccharide with anti-inflammatory and viscoelastic properties. It is a major component of extracellular matrix of the synovial fluid, skin and perilymph. This versatile molecule is involved in the control of tissue hydration, joint synovial fluid maintenance and receptor mediated roles in cell detachment. hyaluronic acid has been reported to improve wound healing in the middle ear, as an alternative sealant in inner ear surgery, as a promoter of postoperative re-epithelization of the mastoid and as a carrier for drug delivery into the inner ear, as well as cell-based therapies.

Synthetic [i.e., Polydioxanone (PDS), polylactides (PLAs), collagen-polyvinylpyrrolidone (CPVP) and polyurethane (e.g., Nasopore)] and Plant-based biomaterials [Oxidized regenerated cellulose (ORC), carboxymethylcellulose (CMC) and sugarcane-cellulose] are other alternative scaffolds.

Chapter 3: Scope of work

3. Scope of work

Material science plays a significant role in medical science. Medical science has tremendous contribution for well-being of people's health. With the advancement of material science with some new material, smart materials, biomaterials there are seen many advancements in medical science simultaneously. Earlier people had to suffer more for any kind of injury like bone fracture, pain etc. But with the advancement of biomaterial, these suffering from injury, pain etc gets reduced gradually. But with the advancement in material science and medical field, there may be some disadvantages of using materials in medical filed. so many researches are going on in these materials to improve its characteristics and applications in human body and many data, theories are available discretely. Perhaps there is no comprehensive study of applications and importance of these metal and materials available. so, the objective of doing this project is to make a comprehensive study of uses of these metal and materials in some specific fields of medical science and to find out how these materials are used in recent time and advancement in each and every field of medical science and what are the advantages and disadvantages of these materials after applications in human body. Then we will find out how to overcome these limitations by technological advancement and will try to upgrade the material for the benefits of society and medical science. we will also try to identify the novel area of each field of medical science.

Chapter 4: Methodology

4. Methodology

• To note down different areas of medical research

We will first try to find out different areas of research in medical science. Medical research includes animal experiments, cell studies, biochemical, genetic and physiological investigations, and studies on the properties of drugs and materials.

• To find out the metal and materials used in that specific field of medical science and thoroughly study that area

Although there are different areas of research in medical science, our main objectives will be finding out the metal and materials used in medical science, since there is various application of biocompatible materials in human body. Like stainless steel, Co-Cr alloys, titanium, hydroxyapatite has importance in orthopaedics. There is different polymer material used in eye implants. Different bi ceramics are used as dental implants etc.

• To find out advantage and disadvantage in utilizing the materials in human body

Although before application of this metal and materials in human body, different criteria are fulfilled like biocompatibility, nontoxicity, but there are many cases where this material showed adverse effect after it is implanted. Like some materials used in orthopaedic surgery gets fractured, some materials do toxic reaction with blood etc. our objective will be to find out the problems in utilizing the metal and materials after they are implanted.

• To have a discussion with the practitioner of specific field and to know about the complications faced by patients in that area

• To find out the scope of improvements

We will try to find out if there are any scope of improvements where the metal and materials fail or show adverse effects with human body. If there are possible ways to improve these problems, we will try to find out what are the different properties in metal and materials, are actually required for the improved usage. And we will try to synthesis those materials for successful usage in biological applications.

Chapter 5: Results and Discussion

5. Results and Discussion

5.1 Materials in Orthopaedic

After reviewing various applications of metals and materials used in Orthopaedic and after discussing with **Dr. Shanti Ranjan Dasgupta**, renowned Orthopaedic Surgeon in Kolkata about many practical cases of complications of patient for these material implant, an attempt for modification of these materials is made theoretically to overcome these limitations by technological advancement.

5.1.1 Titanium

Titanium is the ninth most abundant elements in the earth crust. Titanium cannot be found in pure form, mostly it is found in oxide form. The predominant oxide form of titanium present in the environment is the titanium dioxide (TiO_2). The mineral ore of titanium undergoes different process to make it suitable for biomedical applications. It also undergoes different fabrication process to change its microstructure. Titanium and its alloys have emerged as the excellent candidate for the use of orthopedic biomaterials. Titanium has different phases and alloys. Commercially pure titanium has less than one percent of others alloying element. Titanium alloy grade which is most commonly used in biomedical applications is Ti6Al4V. Pure titanium has two different allotropes. Below 883°C, titanium exists in α-phase (closed hexagonal crystal structure) and above 883°C, a body centered crystal structure of β-phase exists. The α-β phase or metastable β phase has the most desirable characteristics for biomedical applications.

5.1.1.1 Application

a) prosthetic hip and knee replacement

b) spinal fusion instrument

c) fracture fixation devices such as screw, plates etc.

5.1.3 Advantages

a) *Biocompatibility*- Titanium and its alloys have better biocompatibility than other metals. Biocompatibility is the ability of the material to perform with an appropriate host response in a specific application. Titanium has good osseointegration property. The bio inert oxide layer of Titanium that is TiO_2 shields the metal from osseous environment.

b) *Corrosion Resistance*- corrosion resistance is an important property of metallic biomaterials. In biological environment, the implant's structural integrity deteriorates due to electrochemical

corrosion. Titanium has a protective oxide covering of titanium dioxide (TiO_2) those aids to shield it from the biological environment.

c) *Mechanical properties*- the elastic modulus is the resistance offered by material on being deformed under stress. According to Wolf's law, the bone will adjust under which it is put or the other way around. If a bone is replaced with an orthopaedic biomaterial of very high elastic modulus, then the bone will be put under the less pressure than it actually preserves. This leads to aseptic loosening. Although titanium has higher elastic modulus than other cortical bones but its elastic modulus is lower than other metallic biomaterials that are used in orthopaedic applications. Titanium has excellent strength to weight ratio than any other pure metal.

5.1.4 Disadvantages:

Orthopaedic implant failure may cause due to both infectious and non-infectious complications. To avoid this, an ideal orthopaedic biomaterial should have both surface and bulk qualities.

a) The corrosion resistant oxide layer of titanium that is TiO_2 is very thin and barely protects the potential of titanium abrasion particles to the adjacent tissue. The debris particle can cause very serious problems in successful orthopaedic implant and wear particles can be found in the surrounding tissue if unsuccessful arthroplasty occurs. The titanium debris can be found in liver, spleen and lymphatic system. Aluminum promotes bone diseases like osteomalacia and neurological diseases such as Alzheimer's disease, and V ions are cytotoxic. Wear particles produced because of corrosion of titanium can trigger complicated tissue response leading to inflammation and quickens the osteoresorptive process rather than osteogenesis. This leads to loosening of implants, may cause aseptic loosening including micromotion and stress shielding. Patients may suffer from pain and instability while doing some kind of activity.

b) There may be some infectious complications after undergoing arthroplasty and infection of tissue surrounding the implants leading to periprosthetic joint infection (PJI). Bacterial biofilm formation on the implant surface cause infection. If infection spreads quickly, it is required to remove the affected implants from the body which is more complex and painful procedure.

c) pseudotumor formation can cause more complications in a patient when the polyethylene liner fails after total hip arthroplasty. As a result, erosion of titanium alloys femoral stem happens and hypersensitive toxic reaction with the tissue and titanium particles occur.

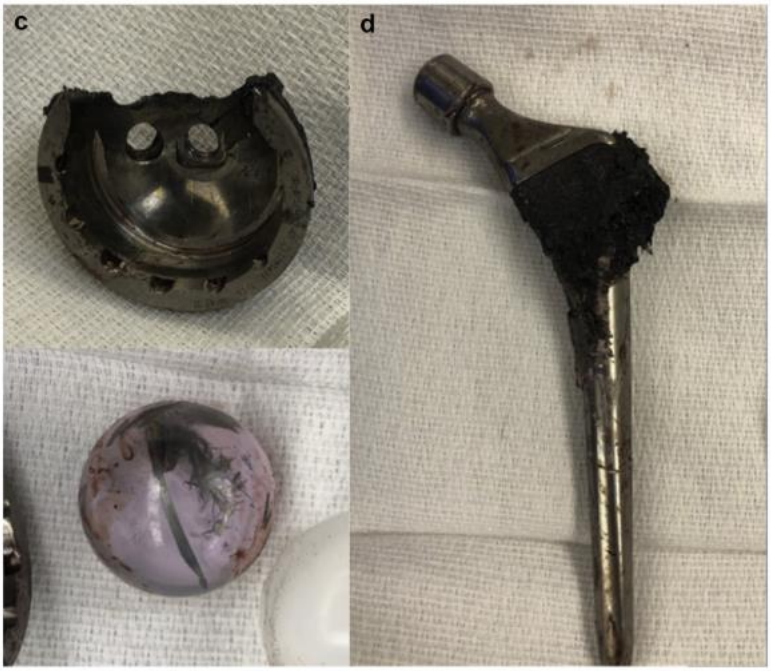

Figure 5.1 Fracture polyethylene liner and femoral head, acetabular hear because of erosion

5.1.5 Modification

For better osseointegration and antibacterial property for titanium implants, different surface modification technique can be applied.

1) *Coating method:*

a) Plasma spraying: Hydroxyapatite which aids osteoconductive, a naturally occurring component of bone. Titanium surface can be coated with HA by plasma spraying method which is a thermal deposition method for better bone growth. Silver, zinc, strontium can be added with hydroxyapatite for coating to make the surface of the titanium anti-infective.

b) Sol-gel deposition: Sol-gel method is used for coating complex shape of orthopaedic implants. Silver nanoparticle coating made by sol-gel method can be applied on titanium surface to minimize the S. aureus adhesion on titanium surface. Sol-gel coating of MgO also enhances biocompatibility and antibacterial properties.

c) Chemical Vapour deposition: In this method, pressurised high temperature gas reacts with the surface of the titanium and forms protective layer on the surface. It has been shown by experiment that TiO_2 coating on titanium surface enhances osseointegration Rabbit in femoral bones in 4 weeks and 12 weeks. Dimethylaminomethyl styrene is a polymer coating which has antimicrobial properties can be deposited by CVD to minimize viable E. coli bacterial infection.

5.1.6 Stainless steel

The 18-8 stainless steel was the first stainless steel used for production of implant because it is tougher and more corrosion resistance than vanadium. Later stainless steel was mixed with small proportion of molybdenum to enhance corrosion resistance property known as 316 stainless steels. 316 stainless steels have 0.08% of carbon content. Stainless steel which has 0.03% carbon content is known as 316L stainless steel, is more corrosion resistance in chloride solution than 316 stainless steels. There is little concentration of chromium in stainless steel to enhance corrosion resistance. 316 and 316L stainless steel are mainly used for implant manufacturing in orthopaedic.

5.1.7 Applications

a) stainless steel is suitable for use as temporary implants like bone plates, hip nails, screw.

5.1.8 Advantages

a) Stainless steel has good corrosion resistance in chloride solution because of its low carbon content (only 0.03 %) which is suitable for in-vivo condition.

b) They have better mechanical properties and low cost compared to other material like titanium.

c) Stainless steel can be easily fabricated for implant production.

d) Elastic modulus is the amount of stress that must be applied for a material to be elastically deformed. The modulus of elasticity of stainless steel is very high. This feature contributes to the rigidity of the structure. This makes stainless steel suitable material for implants in fracture fixation.

5.1.9 Disadvantages

a) Stainless steel has elements like nickel, cobalt, and chromium. These elements are allergens. Release of these elements in the implant site because of corrosion can cause toxic effects in the surrounding tissue or can create hypersensitivity reaction. This adverse reaction causes aseptic loosening leading to repeated surgery. Some elements can get dissolved in the blood stream, posing a risk of long-term harmful effects.

b) Stainless steel orthopaedic implants may undergo static and cyclic loading simultaneously leading to complex stress system in the implants. Stainless steel is mostly used for internal fixation device. So repeated cyclic load is applied on the implant. Also, there are non-metallic inclusions which acts as high stress concentration sites. These stress concentration sites cause micro crack leading to ductile fracture in the implants.

c) Pitting and crevice corrosion can be formed between the screw used in fixation device.

5.1.10 Modification

a) stainless steel orthopaedic materials have tendency to be corroded locally in body fluids. Sign of pitting and crevice corrosion can be found in removed SS implants from the body. To overcome this, hard ceramic coating of Titanium carbonitride (TiCN) is used on the surface of the materials. It has good corrosion resistance, high hardness and better wear resistance. There is a reduction of corrosion by three times magnitude after coating AISI 304 stainless steels by TiCN. It also has non-cytotoxic character for biomedical application.

5.1.11 Cobalt based alloys

Cobalt based alloys is being used since 1907. After that different cobalt-based alloys have been made with cobalt chromium tungsten and cobalt chromium molybdenum. Resistance to wear, corrosion are all advantages of cobalt-based alloys. Cobalt-chromium alloys are divided into two categories: CoCr MO alloys and wrought CoNiCrMo alloys. The castable CoCr MO alloys are used in artificial joints. The wrought CoNiCrMo alloys are used for heavily loaded joints like hip and knee. The CoCr alloys is a solid solution containing up to 65 percent Co. The molybdenum is used to create finer grains, which results in increased strength. The chromium in the alloys increases resistance against corrosion. The CoNiCrMo alloy is also known as MP35N. It contains Ni and Co, each of 35%. The resistance against chloride solution is very high for this alloy. Although the abrasive wear properties of both the alloys are same but The CoNiCrMo is not used for bearing surfaces of joint prosthesis because it has poor frictional properties. The CoNiCrMo alloy is ideal for applications requiring long service life without fatigue fracture i.e., hip joint prosthesis because of their fatigue and ultimate tensile strength. Both of the alloys have good corrosion resistance.

5.1.11 Applications:

a) femoral component in total knee replacement and femoral head in total hip replacement

b) screws in trauma plating systems

c) For the treatment of idiopathic scoliosis, CoCr alloy-based rod is used for its high rigidity.

5.1.12 Advantages

a) Cobalt chromium alloys have very good corrosion resistance property in the in-vivo environment because of formation of chromium oxide layer (Cr_2O_3).

b) this alloy has some improved mechanical properties such as increased fatigue resistance and better resistance to wear. It has high modulus of elasticity (220-230 GPa) which is comparable to stainless steel (200 GPa) but more than cortical bone (20-30 GPa).

c) The biocompatibility and mechanical qualities of cobalt-based alloys are balanced; both are better than stainless steel in resistance against corrosion and strength, but more expensive to design. In terms of corrosion resistance, it is better than stainless steel.

5.1.13 Disadvantages

a) The osteointegration ability of CoCr alloys has been discovered to be quite low. It has been seen in in-vivo condition that when a CoCr alloy-based screw is implanted in sheep, the torque of removing the CoCr alloy is very less than other alloy-based screw. In addition to that, when comparing CoCr alloys with other materials, bone to implant contact analysis is found to be very less in CoCr screws.

b) Allergies and skin dermatitis may be caused by metals discharged from Co-Cr alloy equipment and prosthesis. Cr particles released from the alloys may not react with DNA in in-vitro condition but it can damage DNA-DNA crosslink, DNA-protein crosslink etc. It can also cause chromium induced carcinogenesis.

c) It has been seen that the oxide layer is affected by fretting wear between the CoCr femoral head and Titanium alloy femoral stem due to high cyclic load and repassivation is hampered because of reduction level of oxygen in the interface leading to galvanic corrosion between the alloys.

5.1.14 Modifications

a) Co-Cr alloys are found to have very low ability of osseointegration. Bioactive ceramic coating is used to increase the bioactivity to better integration between bone to implant prosthesis. Hydroxyapatite coating is used to increase bioactivity of the implant and ability to bond with bones. HA has been seen to restrict the release of metal ions of the alloys and also give protection against corrosion. The HA coating can be performed by Electrophoretic Deposition, Investment casting method.

5.1.15 Polymer

Metallic and ceramic materials have been widely used in medical science because of their superior properties like corrosion resistance, elastic modulus etc. But the debris particles generated because of wear of the materials cause allergic reaction and other harmful decease leading to failure of the implants. Metallic materials also have high elastic modulus that can cause aseptic loosening of the implants and stress shielding. As a result, polymer-based materials represent a good alternative of other materials. These materials are cost efficient, self-lubricant etc. Polyethylene, a polymer, is used to make the tibial and patellar components of knee replacements. But polyethylene is mainly suffered from wear. The wear abrasion can be minimised by the use of ultra-highly cross-linked polyethylene (UHXLPE) or ultra-high molecular weight polyethylene (UHMWPE). UHMWPE is used as a bearing surface in total hip joint prosthesis. In this, metal substitutes the bone surface and polymer acts as a substitute for the soft cartilage tissue. Because of its remarkable combination of mechanical and physical properties, it is most extensively utilised in artificial joint.

5.1.16 Applications

a) Acetabular liner b) Tibial insert

5.1.17 Advantages

a) This polymer is chemically inert and has suitable properties like abrasion resistance, impact resistance.

b) UHMWPE has better wear resistance than polytetrafluoroethylene (PTEF). It has very low dynamic friction coefficient (mean value 0.1) in dry condition with alumina surface. Because of the low applied stresses, UHMWPE takes longer to run in.

c) Friction is greatly reduced by the presence of UHMWPE and this is believed to be due to the formation of a lubricating film of UHMWPE in the contact zone.

5.1.18 Disadvantages

a) Although the soft-on-hard contact combination is preferred in joint arthroplasty, the wear debris generated from the UHMWPE bearing surface is a source of many problems, such as aseptic loosening of the joint, initiation of an inflammatory reaction ultimately leading to osteolysis (pathological destruction of bone tissue), etc. For example, the friction of a stainless-steel head against UHMWPE typically produces a 0.2mm/year linear wear rate.

5.1.19 Modifications

a) Improving the wear resistance of the UHMWPE bearing surface is essential and there have many been efforts to do this. the abrasive wear resistance of the material depends on its degree of cross-linking. Its cross-linking rate is observed to increase proportionally to the irradiation doses, improving its wear resistance. However, cross-linking leads to a deterioration in the mechanical properties of UHMWPE and also makes the material more sensitive towards oxidation. A thermal treatment of the polymer is found to eliminate this problem. It is found that the addition of vitamin E (a powerful antioxidant) and other antioxidants also considerably increases wear resistance of the conventional UHMWPE and improves its clinical outcome.

b) The hard counter face and its surface condition also play a significant role in the wear of the polymer. Suitable surface coatings are applied on the counter face surface to maintain a low level of wear. But the durability of these coatings over longer periods is an issue. Harder material, such as ceramics, have also been used as the counter face with improved wear performance. Orientation treatment and the incorporation of fluorinated carbon nanotubes applied to isotropic bulk UHMWPE caused both the reduction of the friction coefficient as well as the decrease of wear rate. Wear rate is found to decrease by about three times compared to initial UHMWPE.

5.2 Materials in Dentistry

After reviewing various applications of metals and materials used in Dentistry and after discussing with **Dr. Samiran Ghosh**, Associate Professor, Dept of Oral & Maxillofacial Surgery at Gurunanak Institute of Dental Science & Research, Kolkata about many practical cases of complications of patient for these material implant, an attempt for modification of these materials is made theoretically to overcome these limitations by technological advancement.

5.2.1 Titanium alloys

Titanium is an excellent material used for different department of dentistry among other dental materials. It has become a popular material for as dental implants meeting all mechanical, chemical biological criteria. The properties of titanium and its surface property for biocompatibility have been explored in several outstanding reviews. Titanium alloys are utilised in conjunction with a variety of other metals in dental patient. The properties of titanium can be influenced by the other metals present in the same oral environment like saliva, fluoride, pH etc.

5.2.2 Applications

a) Endodontic files, Orthodontic wires, brackets, dental implants

5.2.3 Advantages

a) Commercially pure titanium (CpTi) and titanium (Ti) alloys have been used successfully in dentistry many years. These materials have become the material of choice in dental implants due to favourable material characteristics and biocompatibility in the oral environment. The biomaterial properties of CpTi include a combination of mechanical strength, chemical stability as well as its successful integration with the surrounding bone (osseointegration).

b) Additional advantages of using CpTi and/or Ti alloys in dentistry include its high strength-to-weight ratio and resistance to corrosion. Ti has a neutral taste and is considered to be translucent to x rays making diagnostic radiographs feasible in the presence of titanium castings.

c) Ti is also non-ferromagnetic and therefore, patients with titanium implants can safely undergo magnetic resonance imaging. Additionally, the modulus of elasticity of Ti is similar to that of bone, making the bone-to-implant interface closer matching than many other metals.

d) The formation of oxide film TiO_2 is referred to as passivation because the highly dynamic oxide layer subsequently acts as a barrier to protect the underlying metallic Ti from further exposure and chemical reaction (corrosion). Therefore, despite being an active metal, titanium exhibits high corrosion resistance due to the presence of the oxide film.

5.2.4 Disadvantages:

a) Fretting corrosion is caused by friction leading to mechanical wear and damage to the passivation layer on the Ti surface. Fretting between dental implants and bone due to cyclic loading experienced during chewing has been suggested as a cause of Ti corrosion and release of metal debris into tissue. This release of ion and metal debris has been associated with cytotoxicity, inhibition of cell differentiation, phagocytosis of Ti particles by macrophages, inflammation, and neoplastic changes. In addition, the fretting associated cathodic shift in the open circuit potential of CpTi implants alters the electrochemical properties of the CpTi interface and has been associated with reduced biocompatibility.

b) Galvanic corrosion is the most common form of corrosion seen with titanium implants and is accelerated due to an electrical contact with a more noble or non-metallic conductor in a corrosive environment. Dental amalgam is one of the most common choices of direct restorative material for intra-oral use. In the past, mercury toxicity concerns have resulted in an alternative use of mercury free, gallium-based alloy for direct filling material. Although these materials have a passivating film, it is less protective than the one on titanium. When Ti comes in contact with these alloys, it behaves as a noble metal, causing corrosion of amalgam or gallium. Studies show that the galvanic interaction

between titanium and direct filling copper/gallium alloy was minimal. But due to poor corrosion resistance of gallium alloys even small increase in corrosion due to galvanic interaction had a potential of making the corrosion problem severe.

c) Various products like bleaching agents, mouth-rinses and toothpaste containing fluoride are popularly used for esthetic purposes and prevention of plaque and cavity formation. Carbamide peroxide and hydrogen peroxide (H_2O_2) are most common ingredients in bleaching gel. Agents containing fluoride and hydrogen peroxide have been known to reduce corrosion resistance of Ti often resulting in visible discoloration around the implant. fluorides can infiltrate the titanium oxide layer, especially at low pH levels. The corrosion process in titanium due to fluoride results in release of hydrogen as a reaction product, which in turn may cause delayed fracture due to hydrogen embrittlement.

d) It has been seen that metal sensitivity arises after exposure to titanium for some patients in certain circumstances. The emergence of eczema localized to the perioperative facial area after receiving titanium dental implants, in which a complete remission was subsequently achieved by the removal of the titanium material. Thus, it seems that titanium can induce hypersensitivity in susceptible patients and could play a critical role in implant failure.

5.2.5 Modifications

a) One such surface modification is the electrochemical technique. This technique is both simple and cost effective and could be either anodic or cathodic in nature. Adjusting the anodic conditions like current density, voltage and solution concentration can alter porosity and surface roughness of Ti. By anodic oxidation desired chemical composition of the oxide layer can be achieved. In addition, anodic oxidation at high voltages can improve the crystalline structure of the oxide layer on the Ti surface resulting in superior properties of the oxide layer.

Electrophoretic deposition is yet another method of Ti surface modification that uses hydroxyapatite (HA) powders dispersed in a suitable solvent at a particular pH. These particles acquire positive charge in these conditions and coatings are obtained on the cathodic Ti by applying an external electric field. A post-sintering treatment is required to improve the coating properties.

Electrophoretic HA coating on the Ti surface can either be obtained under constant or dynamic voltages. To improve the density of the electrophoretic coating it is usually sintered at a temperature of 600 °C or above.

Another type of electrochemical method is cathodic deposition where HA is formed in situ from an electrolyte containing calcium and phosphate ions. This versatile process has control over

electrophoretic coating thickness, crystallinity and substrate shape. Biocompatibility of Ti can further be improved by obtaining nano-size HA crystals.

b) The effect of phosphorus ion implantation on corrosion resistance and biocompatibility of titanium implants. An increase in corrosion resistance of Ti implanted with phosphorous placed in simulated body fluid was observed after short-term and long-term exposure. The increased corrosion resistance was attributed to the alteration in the chemical composition and structure of the Ti surface layer following the implantation. Transmission electron microscopic examination of the microstructure revealed that after phosphorous ion implantation with a dose of $1*10^{7}$ P^{+}/cm^{2}, the surface layer of Ti became amorphous resulting in increased resistance to corrosion. According to the authors, another reason for increased corrosion resistance was the formation of TiP. phosphorous ion implantation increases corrosion resistance of Ti by amorphization of the Ti surface and by formation of TiP. They further added that at a dose of 1×10^{17} P^{+}/cm^{2} phosphorous ion implantation increased the corrosion resistance of Ti after short-term as well as long-term exposures.

5.2.6 Cobalt chromium alloys

During the 20th century, metal alloys have assumed an important role as restorative materials. Among existing examples, cobalt–chromium (Co–Cr) alloys increasingly began to be used in medicine and especially in dentistry. Their success is mainly due to their mechanical properties such as stiffness, strength and corrosion resistance, thus allowing a high biocompatibility.

5.2.7 Applications

a) Co-Cr alloys are commonly used for the fabrication of metallic frameworks of removable partial dentures and recently have been used as metallic substructures for the fabrication of porcelain-fused-to-metal restorations and implant frameworks.

5.2.8 Advantages

a) Co and Cr dental alloys have the essential characteristic of being resistant to corrosion and oxidation in the body when they are used as inputs for a finished product. Under normal conditions of use, without particular signs of corrosion, the presence of Cr allows the formation of a Cr-based oxide layer on the surface. This layer is valuable, among other things, to protect the Co from oxidation and then to improve the resistance of Co–Cr alloys against galvanic corrosion.

b) A second very important aspect of Co–Cr alloys for their use in restorative materials is their high wear resistance.

5.2.9 Disadvantages

a) Oxide layer of chromium resists the alloys from corrosion. Unfortunately, over time several phenomena can lead to the corrosion of metallic biomaterials such as mechanical abrasion of the protective passivated layer and attack by local acidification due to the presence of certain germs (e.g., Streptococcus mutants). Corrosion can be also related to fragile areas (e.g., lack of material, cracks) due to internal defects during physical metallurgy and processing of Co–Cr alloys. The environment of the oral cavity is thus very favourable to corrosion, with many factors including at least natural agents (air and water, saliva), food contents (chloride ions), sugary drinks, dental plaque, microorganisms, very frequent temperature and pH variations, and the presence of diverse dental prosthetic devices. When the corrosion process starts, Co and Cr ion metals are then released in the oral cavity. Depending on the composition of the alloy, other metal ions may also be released such as Cu, Fe, Fe, Mn, Mo, Ni, etc.

b) Co–Cr dental alloys mainly consist of Co and Cr, but other metals are also present (e.g., Ni, Mo, Mn) and can thus be responsible for undesirable effects. It has been seen release of Co from dental reconstructions and an oral hypersensitivity reaction in a patient allergic to Co. In this case, the patient had a severe and constant urning pain in the mouth, tongue and lips two months after insertion of new dental implants in the upper and lower jaws, but the symptoms disappeared after the implants were replaced. It has been also seen that the patient has suffered for one year from pustules, blisters and scaly erythema on the hands and feet after treatment with Cr–Co crowns, although there were no symptoms in the oral cavity. These symptoms disappeared 3 weeks after removal of the crowns.

c) On 22 September 2017, based on investigations carried out by the European Chemicals Agency (ECHA), the Committee for Risk Assessment (RAC) adopted an opinion on the proposal for harmonised classification of the metal Co. Consequently, the metal Co should be reclassified as CMR 1B substance.

5.2.10 Modification

Soft drinks with low pH cause tooth erosion and dental caries. Erosive enamel demineralization results in surface softening and roughening [24]. Various polymeric films have been tried for physically protecting the teeth against erosion by preventing the direct contact of acidic environment in the oral cavity with the teeth [24–27]. Beyer et al. [25] studied the ability of a polymer modified citric acid solution of propylene glycol alginate to reduce tooth erosion. They found a layer, consisting of two opposing gradients of hydroxyapatite (HA) particles and polymer molecules, helped to reduce the erosion on dental enamel surfaces. The polymers (propylene glycol alginate, highly esterified pectin and gum Arabic) adsorbed on the teeth forming a protective layer on the enamel and dentin that reduced the erosive effects of acid.

5.2.11 Stainless steel alloys

Stainless steel is one of the most widely used materials in current orthodontics. The first evidence of the use of this alloy in the orthodontic field dates back to the mid-1920s, when it was introduced as a material to manufacture wires. The alloy has ever since gained popularity among orthodontists and its further development has led to its widespread use in today's different orthodontic techniques.

5.2.12 Applications

a) Arch wires, brackets, bands, ligatures, tubes

5.2.13 Advantages

a) The three main groups are austenitic, martensitic, and ferritic. Alloys used in orthodontics come from the austenitic type, being 18/8 (18% chromium, 8% nickel, 0.2% carbon and traces of other stabilizing elements) the most widely used. The widespread use of stainless steel in the medical and dental fields resides in different factors, but one of the most important features is its corrosion resistance. This property comes from the addition of chromium to the iron-carbon alloy. This base metal is highly reactive and forms a passive film. This film of chromic oxide resists further attacks from the environment, thus preventing corrosion. Around 11% chromium is necessary to produce corrosion resistance in pure iron, and the proportion increases with the addition of carbon to form the alloy.

5.2.14 Disadvantages

a) It has been found that this alloy exhibits qualitative surface topography changes and a significant decrease in unloading mechanical properties in fluoride solution, which might extend orthodontic treatment time. In this solution stainless steel is slightly affected by hydrogen absorption. The corrosive solution of stainless-steel extracts in acidified NaF artificial saliva can cause u2os cell toxicity and advised to remove wires when applying fluoride or to change the wires after fluoridation to prevent toxicity.

b) The presence of soldered joint increase corrosion susceptibility since they have a tendency to emit electrogalvanic current with saliva and consequently release metal ions. Surface roughness of stainless steel of wires may cause localised corrosion attack. Any cut or abrasion of stainless steel may act as galvanic cell and brazed and soldered joint in orthodontic applications can also form galvanic couples in vivo.

5.2.15 Modifications

a) TiN plating of orthodontic wires can inhibit acid-mediated corrosion, and thus reduce the elution of Ni ions from the wire surface. These results suggest that TiN plating may be useful for the orthodontic treatment of patients with metal allergies. In addition, TiN plating has the potential for use in other dental applications, such as coating the metal parts of removable dentures and for wires to splint the teeth after orthodontic treatment.

b) To enhance the biocompatibility, the stainless-steel wire and brackets can be coated with silver-platinum and polytetrafluoroethylene (PTFE).

5.2.16 Ceramic (Zirconia)

Due to an increasing interest in esthetics and concerns about toxic and allergic reactions to certain alloys, zirconia was proposed as a new ceramic material in the later part of 20^{th} century. It has become a popular alternative to alumina as biomaterial and is being used in dental applications for fabricating endodontic posts, crown and bridge restorations and implant abutments. It has also been applied for the fabrication of esthetic orthodontic brackets. Zirconia is organized in three different patterns: monoclinic (M), tetragonal (T), and cubic (C). Pure zirconia is monoclinic at room temperature and remains stable up to 1170°C. Above this temperature, it transforms into tetragonal and then into cubic phase that exists up to the melting point at 2370°C. During cooling, the tetragonal phase transforms back to monoclinic in a temperature ranging from 100°C to 1070°C. Although many types of zirconia-containing ceramic systems are currently available, only three are used to date in dentistry. These are yttrium cation-doped tetragonal zirconia polycrystals (3Y-TZP), magnesium cation-doped partially stabilized zirconia (Mg-PSZ) and zirconia toughened alumina (ZTA).

5.2.17 Applications

a) dental post

b) crown and bridges

c) abutments

d) brackets

5.2.18 Advantages

a) The most significant advantage of Zirconia dental implants is that they are entirely metal-free. This option is perfect for those who are allergic to metals, and the lack of metal makes it more natural.

b) It is also believed that Zirconia is a great option when it comes to maintaining excellent oral health, specifically gum health. This is because the material is much less susceptible to plaque build-up than other materials. In terms of durability, Zirconia outclasses other materials such as porcelain and ceramic, allowing it to last for a considerably longer time.

c) Zirconia offers maximum contact between the teeth and the jawbone, allowing an effective and efficient fusing process. This means that these implants are better at staying in place.

d) zirconia offers excellent durability and great aesthetics, and it eliminates the need for metal. All of these characteristics make Zirconia highly desirable for many patients. However, as we have said earlier, this option is not meant for everyone.

5.2.19 Disadvantages

a) The disadvantages of zirconia crowns are minimal. The toughness of the material has raised some concerns about friction against the tooth root and wearing down opposing teeth. Frequent check-ups, however, help to reduce the possibility of damaging opposing teeth.

b) One of the biggest drawbacks of choosing zirconia dental implants is low-temperature degradation as the product ages. This could potentially result in the mechanical properties of the material becoming degraded, reducing the strength, density, and toughness of the material.

5.3 Pain Management

After reviewing various drugs used in pain management and after discussing with **Dr. Subrata Goswami**, Deputy Director (Medical), Directorate of ESI (MB) Scheme, Department of Labour, Government of West Bengal, about many practical cases of complications of patient for taking these drugs for long term, an attempt is made theoretically by giving an idea of using drug release by targeted nanoparticle to reduce the side effects of these drugs.

There are different drugs which are used to reduce pain is given in table 5.1

Serial No	Pain Type	Medication used
1)	Headache	paracetamol /acetaminophen, NSAIDs
2)	Migraine	Paracetamol, NSAIDs
3)	menstrual cramps	NSAIDs
4)	minor trauma, such as a bruise, abrasions, sprain	Paracetamol, NSAIDs
5)	severe trauma, such as a wound, burn, bone fracture, or severe sprain	opioids
6)	strain or pulled muscle	NSAIDs, muscle relaxants
7)	minor pain after surgery	Paracetamol, NSAIDs
8)	severe pain after surgery	opioids
9)	muscle ache	Paracetamol, NSAIDs
10)	toothache or pain from dental procedures	Paracetamol, NSAIDs
11)	kidney stone pain	paracetamol, NSAIDs, opioids
12)	pain due to heartburn or gastroesophageal reflux disease	antacid, H2 antagonist, proton-pump inhibitor
13)	chronic back pain	paracetamol, NSAIDs
14)	osteoarthritis pain	paracetamol, NSAIDs
15)	Fibromyalgia	antidepressant, anticonvulsant

Table 5.1: Table of different applications of drugs used in pain

5.3.1 Chemical responsible for pain

NSAIDs work by blocking (inhibiting) the effect of chemicals (enzymes) called cyclo-oxygenase (COX) enzymes. COX enzymes help to make other chemicals called prostaglandins. Some prostaglandins are involved in the production of pain and inflammation at sites of injury or damage. A reduction in prostaglandin production reduces both pain and inflammation. Not all NSAIDs are exactly the same, and some work in slightly different ways from others.

Paracetamol - No one really knows for sure exactly how paracetamol works. But it is also thought to work by blocking COX enzymes in the brain and spinal cord (central nervous system). Paracetamol is used to treat pain and to lower a high temperature. However, it does not help with inflammation.

Opioids work by binding to certain receptors (opioid receptors) in your central nervous system, your gut and other parts of your body. This leads to a decrease in the way you feel pain and your reaction to pain, and it increases your tolerance for pain.

5.3.2 Disadvantages

a) Conventional local anaesthetics are not specifically Na_v channel blockers and if they leak into the circulatory system or CNS, they can cause rare but life-threatening systemic toxicity. Neurotoxins

are also powerful and specific Na_v blockers, but they have fewer significant side effects. When local anaesthetics are combined with Na_v blockers like tetrodotoxin (TTX), Guanidinium and saxitoxin (STX) they can prolong the anaesthesia. Because of their systemic toxicity, the use of these neurotoxins is limited.

b) NSAIDs and acetaminophen are not harmful in low doses, but long-term use can cause adverse effects in the stomach and liver, respectively. If acetaminophen drug is overdosed, it can cause Drug-induced acute liver failure which has a high morbidity and mortality rate.

c) Morphine is a type of opioid that has a long duration of action. It has some adverse effects. It causes release of histamine which causes bronchospasm and hypotension and respiratory depression resulting in a reduced response to arterial carbon dioxide tension. Morphine may also cause venous pooling and orthostatic hypotension by lowering sympathetic nervous system tone, which causes decreased tone in peripheral veins and causes venous pooling. Morphine will cause biliary smooth muscle spasms, sphincter of Oddi spasms, and decreased intestinal motility, resulting in constipation, in the digestive tract.

d) FDA recently has released a public health advisory about adverse effects in nursing infants whose mothers are taking codeine and appear to be ultra-rapid metabolizers of codeine can have higher level of codeine in their breast milk and natal neonate respiratory depression. The lowest effective dose for the shortest length of time should be used when giving codeine-containing drugs to breastfeeding moms.

e) Sedation, nausea and vomiting, dizziness, headache, and respiratory depression are all common side effects of buprenorphine. It may hasten withdrawal in patients who have established physical dependency after receiving repeated doses of a morphine-like agonist. Only relatively large dosages of naloxone can reverse buprenorphine's respiratory depressive effects.

f) Propoxyphene is a Schedule IV medication that is a modest opioid agonist used to treat mild to severe pain. When propoxyphene is taken with other medicines that cause drowsiness, it can cause dizziness, sedation, weakness, and falls, as well as moderate visual abnormalities, agitation, paradoxical excitement, and sleeplessness, all of which can lead to drug-related deaths.

g) Aspirin should not be given to children under the age of 18. It can lead to Reye's Syndrome, which is a life-threatening condition.

5.3.3 Modifications

Increase advertence of chronic pain as a result of injury or disease has prompted drug manufacturer and pharmaceutical researchers to develop and manufacture better and more targeted pain medicine.

But the overuse of pharmaceutically available drugs shows adverse consequence and side effects which can increase suffering of patient and lead to reduction in efficacy of the pain medications. Nanotechnology has been used in the realm of drug delivery to improve treatment efficiency and reduce negative effects. Nanomaterials have a number of benefits for chronic pain management, including regulated release, longer circulation time, and less adverse effects. Strategies for chronic pain alleviation have sprung out as a result of the advancement of nanotechnology, utilising a variety of nanomaterials and surface alterations. Nanomaterials can be developed to have intrinsic qualities that reduce chronic pain in addition to being used as medication delivery vehicles.

Nanomedicine intends to use nanotechnology to increase the efficiency and safety of pharmaceuticals by encapsulating them in biocompatible nanocarriers like nanoparticles, liposomes, micelles, and dendrimers. The size, shape, surface charge and doses of nanoparticle drug delivery system can be tuned to extend circulation of drug and targeted delivery. To transport the medicine across blood brain barrier and to CNS, nanoparticle drug delivery system surfaces can be manipulated with cell membrane permeable peptide or ligand. By controlling spatial localization and decreasing dosage and adverse effects, NDDSs can improve medication efficacy. The therapeutic potency of a nanocarrier can be increased by comprising numerous analgesics or small compounds with the nanocarrier which may aim for receptor causing pain. Such techniques may be able to circumvent the redundancy that exists in critical processes like pain transmission. Systemic, neuropathic, regional, and disease-related pain are being treated with NDDSs, which have a lower risk of adverse effects.

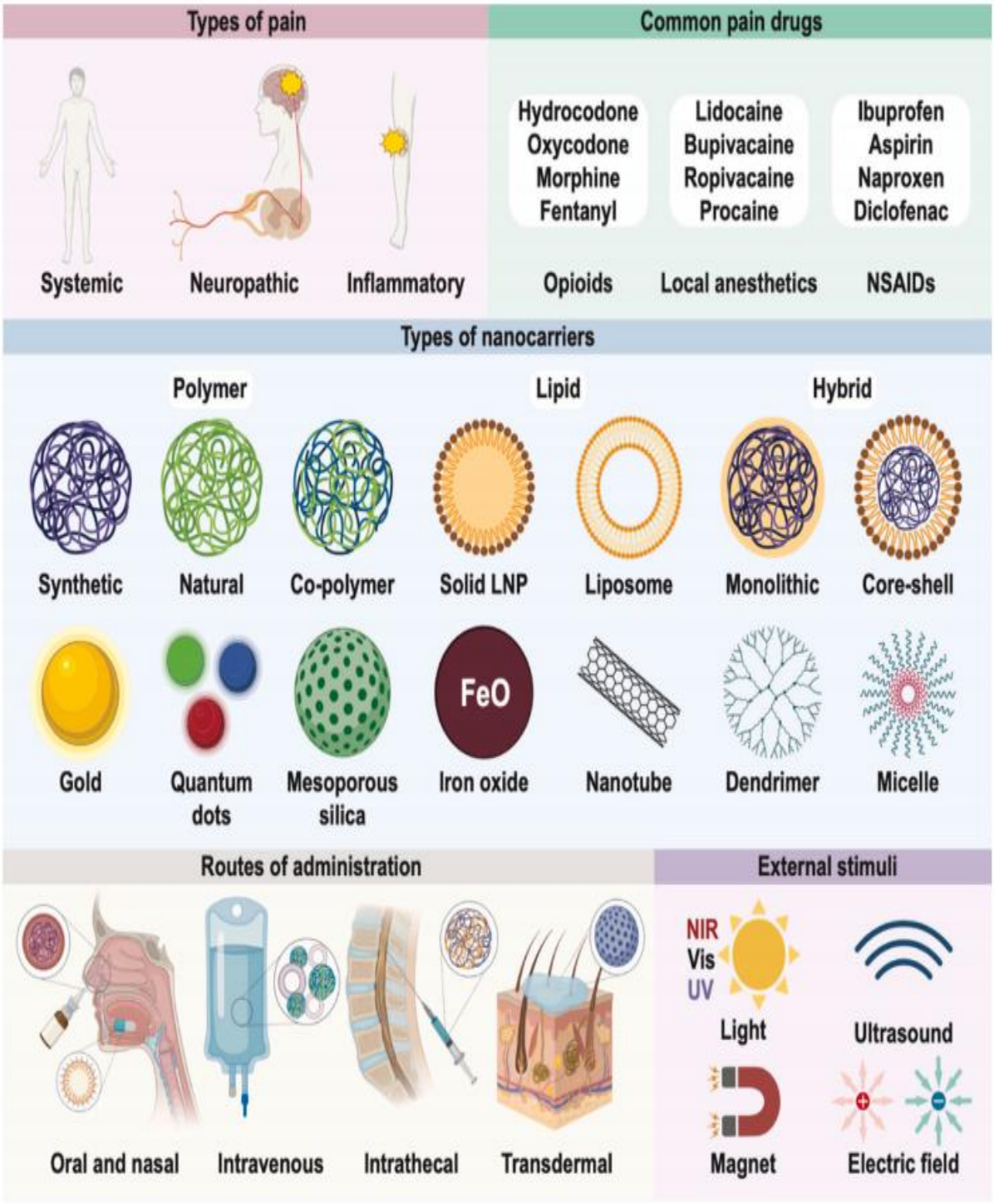

Figure 5.2 Different types of nanocarrier for pain management

a) Local injection of hollow silica nanoparticles loaded with tetrodotoxin (TTX) to the sciatic nerve increased the duration of nerve block while decreasing toxicity. The nanoparticles could penetrate the sciatic nerve in a size dependent manner, enhancing efficacy while improving safety. Saxitoxin (STX) and dexamethasone have also been encapsulated in liposomes for treatment of neuropathic pain; a single percutaneous injection of STX-dexamethasone nanoparticles provided a nerve block

that lasts for about a week in a rat spared nerve injury model. Crotoxin, a rattlesnake venom-derived neurotoxin with prolonged anti-inflammatory and antinociceptive activity, was encapsulated in inert SBA-15 MSNs to treat neuropathic pain, resulting in reduced toxicity of crotoxin and enhanced analgesic effect after subcutaneous and oral delivery in a mouse neuropathic pain model.

b) Drug-induced acute liver failure has a high morbidity and mortality rate, with the leading cause being acetaminophen overdose. Milk thistle-extracted silymarin has shown hepatoprotective properties due to its antioxidant, anti-inflammatory, and antifibrotic effects. Silymarin nanoparticles entrap acetaminophen via nanoprecipitation, and upon intraperitoneal injection, glutathione is generated to counter hepatic damage. In an animal model of acetaminophen-induced hepatotoxicity, no death occurred even when the drug was administered after established hepatic necrosis. Similar NDDS-based approaches can reduce the side effects of long term NSAID use for chronic pain.

c) Osteoarthritis is a disease of the cartilage and bone and is marked by chronic pain. Most osteoarthritis drugs are aimed at mediating this pain. Osteoarthritis is typically treated with NSAIDs, cyclooxygenase-2 inhibitors, or experimental therapeutics such as MAPK inhibiting drugs. Targeting these drugs to the cartilage matrix and subchondral bone can be achieved by using nanocarriers (< 40 nm diameter) with positive surface charges, such as micelles and dendrimers. Targeting the cartilage surface, synovial membrane, intra articular space, or infrapatellar fat pad requires larger nanoparticles (> 60 nm) to avoid penetration into cartilage, making liposomes, high-generation dendrimer micelles, and other larger nanoparticles more suitable nanocarriers for these applications. The combination of osteoarthritis drugs with appropriate nanocarriers for targeting will lead to more effective treatments of osteoarthritis-associated pain with fewer side effects.

d) Metastatic cancer can be excruciatingly painful, and the success rate of treatment is low. Between 30% and 50% of patients with tumours receiving active treatment and 70–90% with advanced-stage disease experience chronic pain. Prostate cancer tends to metastasize to the bone, where it often becomes untreatable and causes intractable pain. alendronate-conjugated PLGA-cabazitaxel nanoparticles is developed to target bone metastases to treat bone pain. In mice orthoptic bone tumour models, the targeted nanoparticle-treated group showed lower pain as well as reduced tumour burden and improved maintenance of bone structure than the free drug-treated group, alleviating long-term pain and other complications.

e) The overproduction of reactive oxygen species (ROS) at sites of inflammation can result in chronic pain; consequently, nanomaterials that consume ROS are a promising avenue for pain relieve. Along these lines, employed fullerol nanomaterials, which are known to consume ROS, to protect inflammatory sites and relieve the pain

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5.4 Trace elements

After reviewing various function of trace elements in our body and after discussing with **Dr. Pinaki Sarkar**, Professor of Medical Biochemistry at West Bengal Medical Education Service, about many practical cases of complications of human for taking these trace elements as supplement, an attempt is made theoretically by giving an idea for reducing the side effects of these trace elements supplement.

The human body is composed of elements which can be roughly divided into abundant elements and trace elements. Abundant elements consist of the major elements that are involved in the formation of covalent bonds and are important constituents of tissues (oxygen, carbon, hydrogen, nitrogen, etc.), and semi-major elements, which often exist in the ionic state, and are involved in functions of the living body through maintenance of osmotic pressure and membrane potentials (potassium, sodium, etc.). Major elements account for 96% of the total body weight, and the semi-major elements account for 3 to 4% of the total body weight. Deficiency of major elements can lead to nutritional disorders, and their presence in excess can cause obesity. Deficiencies or excess states of semi-major elements often result in water and electrolyte abnormalities. Essential trace elements of the human body include zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn), and molybdenum (Mo). Although these elements account for only 0.02% of the total body weight, they play significant roles, e.g., as active centres of enzymes or as trace bioactive substances. A major outcome of trace element deficiencies is reduced activity of the concerned enzymes. However, since each trace element is related to so many enzymes, deficiency of a single trace element is often not associated with any specific clinical manifestations, but rather manifests as a combination of various symptoms. Because of the presence of trace elements in very small amounts and the absence of specific clinical features associated with their deficiency, it is often difficult for clinicians to identify deficiencies of some particular trace elements.

5.4.1 Problems associated with trace elements

a) Zinc toxicity from the supplement may lead to nausea and vomiting, a loss of appetite, abdominal pain, diarrhoea. Sometimes people have to take zine for long term for some disease but it may cause low levels of high-density lipoprotein (HDL), or “good,” cholesterol, decreased immune function, copper deficiency.

b) Milk of magnesia or magnesium hydroxide Mg (OH)2 is used to neutralise excess stomach acid as an antacid. Most common side effects of magnesium hydroxide are Diarrhoea.

c) It has been seen that iron supplement consumption may reduce zinc and copper absorption and imbalance of other trace metals.

d) Taking lower doses of selenium for a long time can increase the risk of higher fasting plasma glucose and glycosylated haemoglobin levels.

f) The reduction of antioxidant potential which occurs because of copper supplement.

5.4.2 Modifications

a) Inorganic iron is absorbed into mucosal cell by a protein linked divalent metal ion transported and accumulated intra cellularly as ferritin. zinc and many divalent metal ions compete for absorption when taken together reducing bioavailability of each other.

b) Magnesium salts are laxative. So excessive use of magnesium containing antacids may cause diarrhoea. Concomitant use of aluminium containing antacids which have inherent property of causing constipation can alleviate this problem. Also, magaldrate a combination of aluminium and magnesium salts which release them in a sustained manner, can be a good alternation

c) Therapeutic benefits of selenium not yet established. Although it has been used as a dietary supplement as a combination. It is a structural component of many enzymes and constitutes a fundamental in front of antioxidant defences. As a result, in low doses, it is actually beneficial in diabetes. It is documented that selenium in high doses can increase insulin resistance but effects on glucose level is not establish.

Conclusion and Future Prospects

This present thesis is an attempt to find the Uses of metals and materials in some specific fields of medical science like orthopaedics, dentistry, pain management etc. and to find out some of the areas where complications happen and give an idea to overcome these complications. Currently the surface modification technique that has shown the most commercial success has been plasma spraying . Problems encountered with metal-on-metal hip implants have stressed the importance of ensuring a medical device is thoroughly tested before it reaches a widespread clinical setting. It appears that the discussed methods of improvement or modifications could be applied on the surface of the materials and can be observed in in-vivo and in-vitro conditions. However, what appears to be limiting the progression of the field is commercial integration and thorough clinical evidence.

Any of the aforementioned surface technologies discussed should ideally be highly reproducible if it is to have the scalability required to reach a commercial setting. In this regard, it is understandable as to why plasma spraying has been commercially viable. Laser surface modification in this respect could be promising method due to its fast, robust, and reproducible nature. Furthermore, with an expanding understanding of the biological processes that govern implant success, there is a growing potential for the use of biologically active coatings. It is envisioned that future marketed material for orthopaedic and dental products could synergistically utilize a biologically active coating and other surface technology in an effort to ensure not only osseointegration, but also sufficient antibacterial properties, thus comprehensively possessing the key attributes for an ideal material for orthopaedic and dental use: mechanical strength, biocompatibility, and resistance to infection.

Nanomedicine has become an important field in therapeutic research, but nanotherapeutics have only begun to be explored in the context of pain management, in part due to the complex nature of pain. Current therapeutics for chronic pain do not provide adequate relief and many debilitating side-effects. Advances in nanomaterials and nanoparticles are improving the targeting and detection of the molecular sources of pain to reduce dosage and improve long-term efficacy and safety.

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