Chapter-2

Literature Review

2.1 Bone Tissue

The human skeletal system has 206 bones. These bones are divided into four categories: long bones, flat bones, short bones, and irregular bones. The primary functions of bone tissues are as follows (Standring 2015, Florencio-Silva et al. 2015):

1. Mechanical functions: that sustain and secure essential organs and also the nervous system. Bones enable the transmission of forces from one portion of the body to the other. The capabilities of bone in terms of its mechanical parameters include its ability to balance the stiffness (reduced elastic property to minimize the stress) and ductile behaviour (that absorbs shock vibrations thereby reducing fracture risks).

2. Metabolic functions: bone is an evolving tissue that is constantly regenerating due to mechanical loads. Mineral salts are stored or released as a result of this remodeling process. Therefore, the bone contributes to the body's homeostatic metabolism.

3. Hematopoiesis: Bone marrow, contained within the bone's medullary cavity, helps to generate blood cells.

2.1.1 Bone structure and composition:

Bone structure:

Bones can be considered as composite substances made up of connective tissues with an internal part made up of spongy bone also known as trabecular/cancellous bone, whereas the external part comprising of the compact bone usually called cortical bone (Tang 2017, Piekarski 1973). Depending on these bones, the relative density ranges between 20-80% throughout the skeletal system. The porosities also vary between the inner and outer layers of bone (i.e., cancellous bone is porous, whereas cortical bone is compact) (Samuel et al. 2009). Cortical bone supports and protects against mechanical stress, whereas cancellous bone allows for metabolic processes. Figure 2.1 illustrates the hierarchical structure and composition of bone from macro scale to sub-nano scale.

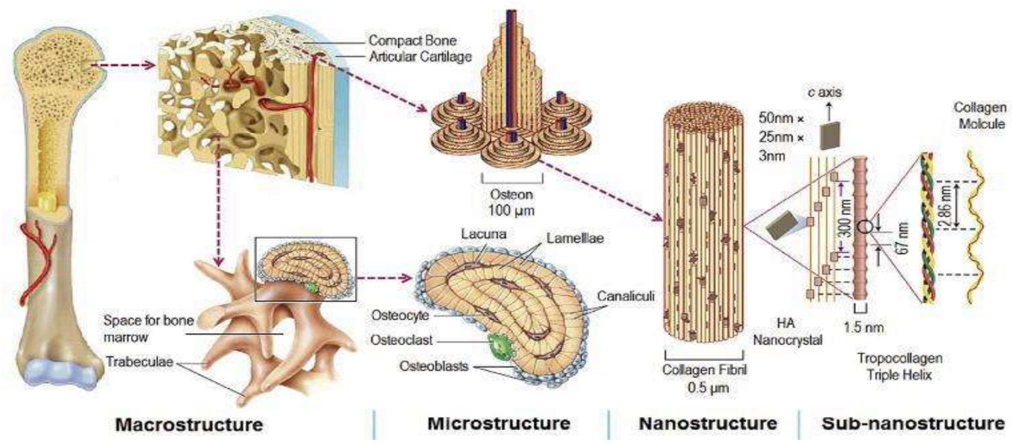

Figure 2.1: Hierarchical structure of bone ranging from macro to sub-nanostructure scale (Mullen et al. 2010)

Cortical Bone:

Cortical bone is a thick and complicated structure that accounts for 80 percent of skeletal weight. The canals and resorption cavities that contain blood vessels and nerves, contribute to the cortical bone porosity of 3-12%. Cortical bone is primarily composed of osteons, which are lamellar structures made up of collagen fibrils organized in concentric rings. Lacunae and interstitial tissue fill the space between the osteons. Lacunae contain osteocytes that are bone cells and interact through microscopic channels called canaliculi. Cortical bone primarily serves as a protective layer, and its thickness is determined by location, mechanical stress, and other variables (Wang et al. 2016, Wegst et al. 2015).

Cortical bone is present near the bone's periphery and encloses the medullary canals containing the cancellous bone as well as the bone marrow. It is responsible for the dense diaphysis walls of long bones like femur, tibia, etc. but relatively thin walls in case of short and flat bones like maxilla and mandible (Tang 2017, Samuel et al. 2009).

Cancellous Bone:

The cancellous bone also called trabecular bone has a porosity of 50-90% and is found within long cortical bones. Figure 1 depicts the interconnection of rod and plate-like structures known as trabeculae. Each trabecula is made up of several lamellae with a total thickness of 200-400 m, allowing nutrients to diffuse without the presence of the Haversian system (no blood cells or osteons) (Khurana 2009). Bone marrow fills the pores in trabecular bone (Wang et al. 2016, Wang et al. 2010). Cancellous bones weigh less, have a larger surface area, and are less stiff. They behave as space filler structures without increasing the bone weight.

Trabecular bone is enclosed within the cortical bone and exists in limited amounts in the central diaphyseal region of long bones whereas it constitutes a larger proportion of their metaphyses and epiphyses to absorb the loads (Currey 2002).

Bone composition:

Human bone resembles a complicated composite structure consisting organic matrix, inorganic minerals, water, and bone cells. The organic material of the bone accounts for a dry weight of 40% and mainly contains Type I collagen. The inorganic composition is mostly composed of hydroxyapatite (HA), a crystalline type of calcium phosphate. As a result, human bone serves as a reservoir for the regulated discharge of calcium and phosphate. There are other minerals such as carbonates, fluorides, and magnesium (Khurana 2009).

2.1.2 Bone cells

The cells that contribute to bone formation and those which comprise a naturally stable human bone are osteogenic cell, osteoblast, osteocyte, osteoclast, and bone lining cell (Florencio-Silva et al. 2015). Osteoblasts predominantly act as bone building cells whereas osteoclasts are responsible for disintegration of bone matrix protein, commonly known as "bone resorption". Osteogenic or osteoprogenitor cells replicate to make osteoblast cells. Osteocytes provides bone tissue metabolism by exchange of wastes and nutrients with bloodstream. Bone lining cells in the inactive state act as osteoblasts and are found on the surface of bone, but when triggered, they enhance the osteoblast progenitor cell growth as well as transmit the signal that stimulates bone resorption and bone regeneration.

These cells cooperate to regenerate the bone tissue, however since the process of cell destruction is more than cell formation, it leads to a decrease in bone density, which reduces bone strength and could eventually lead to osteoporosis.

2.1.3 Bone growth and modeling:

These are simultaneous processes that are influenced by various local factors. During bone growth, the addition of the outer layer of the bone (periosteal bone) is faster compared to the removal of the internal surface of the bone (endosteal bone). Modeling of the bone influences the shape, size, anatomy, formation of joints, and overall growth rate of the bone. The modeling of bone (i.e., increase in dimensions, mass, and strength of the bone) is initiated once a bone reaches its load-bearing capacity. Additionally, even after the complete growth of the bone, remodeling continues with the replacement of old bone tissue with a new one and the repair of injured bone with new bone tissues. The remodeling is mainly dependent on two types of cells, osteoclasts which help in the removal of old bone, and osteoblasts which help in the formation of new bones as shown in Figure 2.2. The modeling and remodeling are influenced by mechanical loads, exercise, lifestyle, and also diet (Syahrom et al 2018, Tortora and Derrickson 2010).

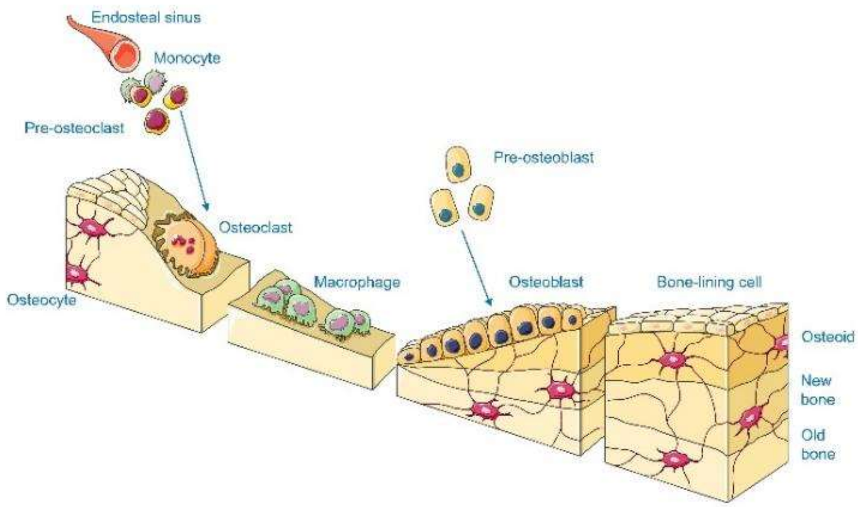

Figure 2.2: Bone remodeling process (from Servier medical art)

2.1.4 Mechanical Properties of Human Bone:

As mentioned earlier, bone is a complex hierarchical system that influences the mechanical properties of each hierarchy. Also, mechanical properties of bone depend on several factors such as age, mineral composition, gender, anatomical location, a diseased condition such as osteoporosis, etc. (Wang et al. 2010, Morgan et al. 2018). Also, some of the external factors that influence the mechanical properties are loading direction and strain rates (Wang et al. 2010, Wu et al. 2014). Reviewing the previous reports on mechanical properties of bone has shown a substantial amount of variability which is obvious in the above-mentioned regions. However, Table 2.1 shows the typical mechanical characteristics of bone at the macroscopic level comprising cortical and trabecular bone adopted from the most cited research.

Cortical or compact bone is considered to be transversely isotropic since the osteons are oriented along the longitudinal direction of the bone (Cowin and Telega 2003). A typical stress-strain curve of the cortical bone is shown in Figure 2.3. The curve has a linear elastic region followed by a plateau depending on the loading rate, which affects the measured properties of cortical bone.

Table 2.1: Mechanical properties of human bone (cortical and cancellous bone) (Dziaduszewska and Zieliński 2021)

Properties	Cortical Bone	Cancellous Bone
Porosity (%)	3 - 12	50 - 90
Density (g/cm^3)	1.85 ± 0.06	0.30 ± 0.1
Compressive Strength (MPa)	130 - 193	4 - 12
Tensile strength (MPa)	50 - 150	10 - 20
Stiffness (GPa)	14.7 - 34.3	0.1 - 2.942
Young modulus (GPa)	3 - 30	0.02 - 0.5

The curve indicates that at low strain rates, the hierarchy of the cortical bone delays the crack propagation there by increasing the toughness (Wu et al. 2014, Park and Lakes 2007).

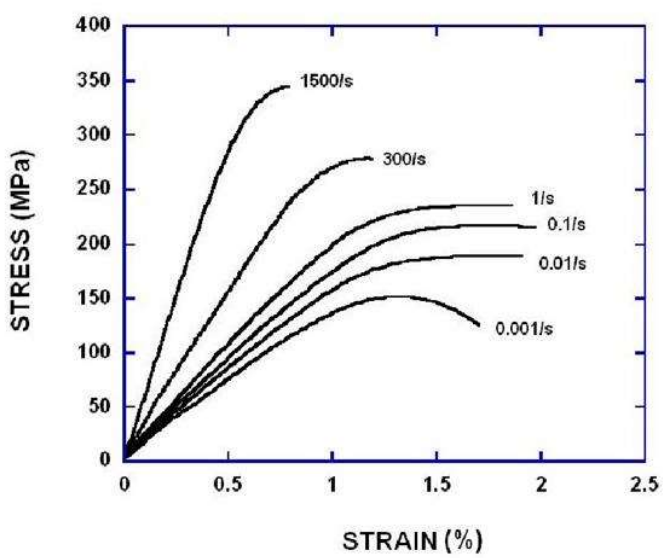

Figure 2.3: Stress-strain curve of cortical bone loaded at various strain rates (Novitskaya et al. 2011)

Trabecular bone has a higher porosity than cortical bone which leads to reduced stiffness but this results in a higher surface area which helps in the remodeling process. The strength and stiffness of cancellous bone are highly dependent on its density. The typical stress-strain curve for the cancellous bone is shown in figure 2.4 which shows a substantial amount of variation in the change of cancellous bone densities. Observing the particular stress-strain curve clearly shows the three regions, as linear elastic regions, plastic-collapse, or yielding with a plateau, followed by the densification of bone which increases the stress.

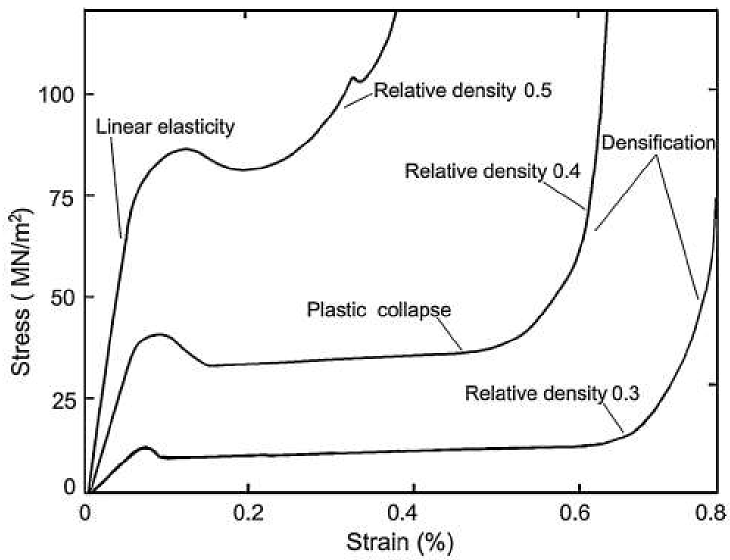

Figure 2.4: Stress-strain curve of trabecular bone for different relative density (Shim et al. 2012)

Gibson et al. provided a graphical representation of the variation of Young's modulus with a density of bone as shown in Figure 2.5 (Gibson et al. 2010). Wang et al. have compiled a database for the mechanical characteristics of cortical as well as trabecular bones by considering the effect of various parameters such as species, location, age, and loading direction. (Wang 2010).

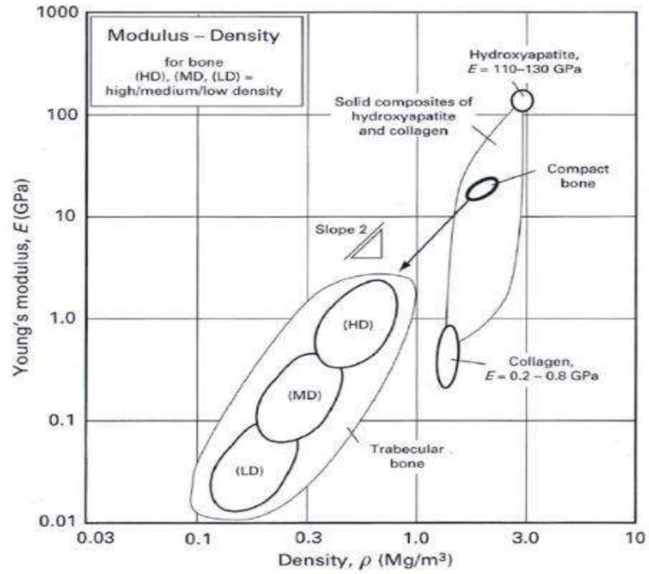

Figure 2.5: Variation of Young's modulus with density of human bone (Gibson et al. 2010)

2.2 Bone Situations Needing Repair

As mentioned earlier, the human skeletal system experiences complex loads, and the bones model and remodel themselves based on the mechanical load applied. Despite the strength and stiffness of the bone, they are vulnerable to fractures or breaks. Joint diseases, like osteoarthritis and rheumatoid arthritis; bone diseases, like osteoporosis and consequent frailty fractures and trauma-related fractures, bone tumors; and spine diseases, such as intervertebral disc degeneration, are primarily caused by continuous discomfort that limits motion, flexibility, and complete functional strength, significantly decreasing the work efficiency. Musculoskeletal problems have a worldwide impact, and considering the severity of 658 million cases in which lower back pain is the largest source of disability which may occur due to many physiological, pathological, and trauma-related causes. In this regard, WHO designated the years 2000-2010 as the Bone and Joint Decade (WHO Scientific Group.2003).

People of all ages, from all walks of life, are impacted by musculoskeletal disorders. Factors that significantly contribute to the total burden of musculoskeletal disorders include fractures

(436 million people globally), osteoarthritis (343 millions), additional injury (305 millions), amputation (175 millions), and rheumatoid arthritis (14 millions). Figure 2.6 shows different types of skeletal disorders and their treatment with metal prosthetics.

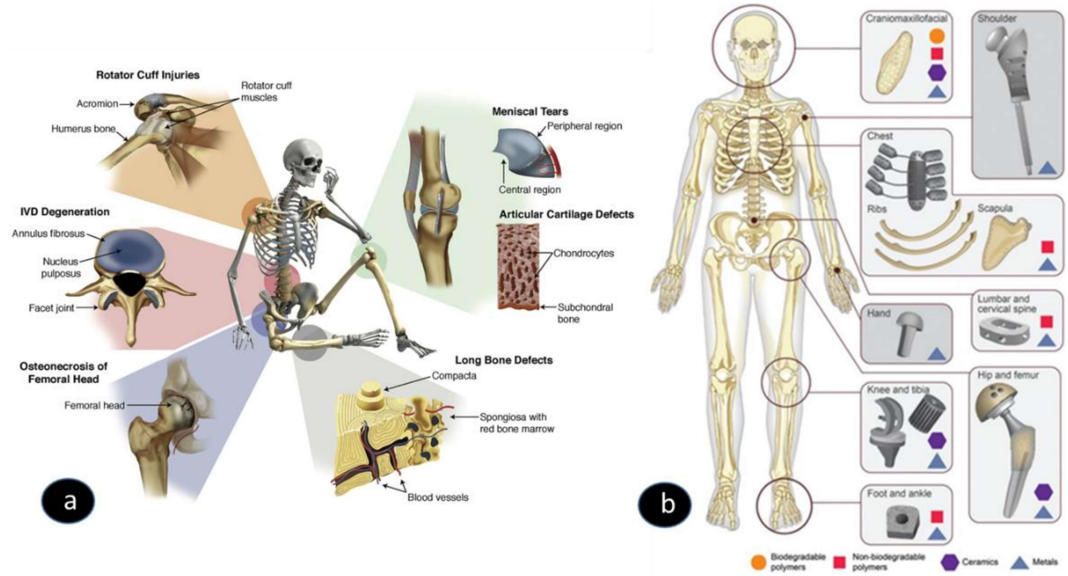

Figure 2.6: Skeletal defects are treated with prosthetic implants. (a) Examples of skeletal tissues with major risk of injuries and defects.(Loebel and Burdick 2018). (b) Orthopaedic implants used to treat bone defects. (Garot et al. 2021)

Since the frequency of bone diseases advances with age, young adults are often affected, frequently in their optimal working years. Although non-surgical therapies are used by a vast majority of patients to reduce the discomfort caused by such diseases, surgery is the preferred and end-stage choice of treatment in serious conditions of discomfort, such as bone fractures, osteoarthritis, and bone tumors. (United States Bone and Joint Initiative., 2014). Regardless of the self-healing potential of bone tissue, about 5-10% of fractures cannot be self-healed or repaired (referred to as non-unions) by conventional methods such as plaster casts and needs costly surgical procedures (Einhorn 1995) Two types of critical bone conditions that require clinical treatment include bone fractures and segmental bone defects which are discussed below.

2.2.1 Fractures

Bone stiffness allows it to withstand external mechanical forces. Exceeding the values of external forces from the resistance potential of bone material causes a fracture. Fractures appear in different forms as shown in Figure 2.7. They occur as a result of a trauma, and the complexity of the damage determines the level of medical interventions. Overuse is another reason for the occurrence of fractures (Fazzalari 2011)

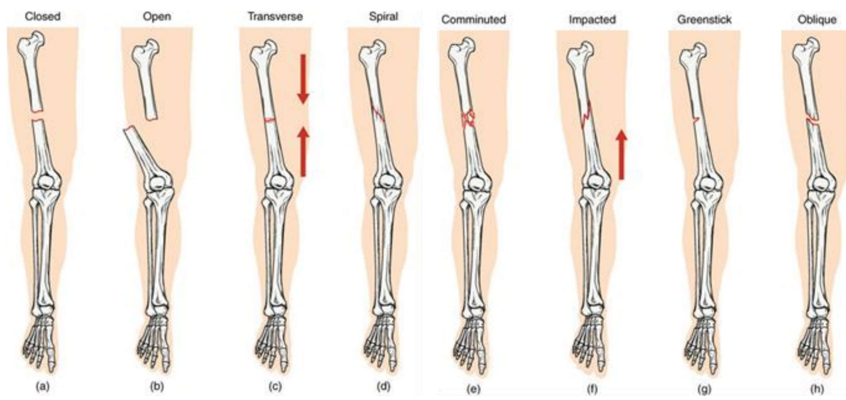

Figure 2.7: Different types of bone fractures (Diseases and disorders from CNX Anatomy & Physiology Textbook)

Fractured bone healing can be characterized as a complicated natural process with three intermediate steps: inflammatory, tissue repair, and bone formation stage (figure 2.8) that occurs for relatively small bone deformities (Wang et al. 2017, Marsell and Einhorn 2011, Fazzalari 2011).

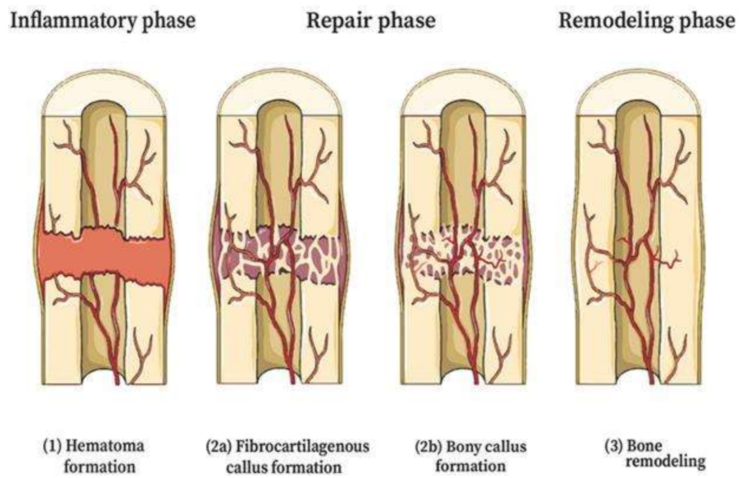

Figure 2.8: bone fracture healing (Anastasio et al. 2021).

When the bones are unable to repair the fracture and recover completely within 6-9 months following the trauma, it is classified as non-union (Buza 2016). The non-unions arise spontaneously in SBDs and may be influenced by pathological diseases like pseudo arthrosis, bone tumour, or osteoporosis (Sparks et al. 2020). Non-unions are caused by the soft callus that are unable to convert into a calcified bone matrix, necessitating subsequent surgical intervention for recovery (Mora et al. 2006, Holmes 2017).

2.2.2 Segmental Bone defects

The bone remodelling process allows bone tissue to recover spontaneously when the damage is minor in size. However, bone loss might be significant owing to traumatisms or diseases, impeding normal recovery. The bone tissue is unable to regenerate itself after a certain size, necessitating surgical treatments. This is known as a segmental bone defect (SBD) or critical size defect (CSD) and shown in figure 2.9.

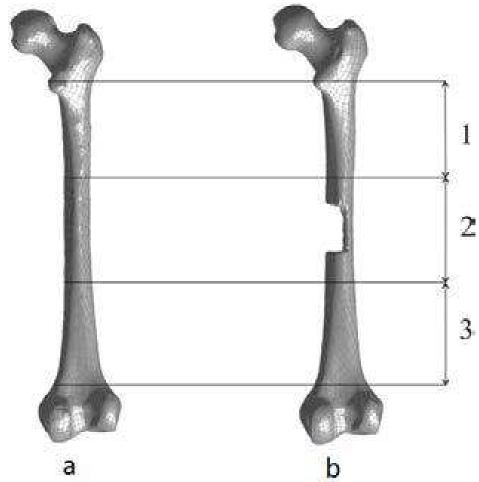

Figure 2.9: 3D model of human femur bone showing a) Intact femur b) segmental bone defect (Bosiakov et al. 2017).

Such defects are influenced by the bone defect site, surrounding conditions of its tissue, the age of patients, as well as the existence of any medical conditions or diseases (Fazzalari 2011). These defects can be induced by significant traumatic as well as pathophysiological conditions (Reichert et al. 2009, Wildemann et al. 2007). Because of the bone loss caused by such defects, the process of vascularization and bone formation get disrupted, eventually leading to spontaneous bone fractures that are impossible to heal without surgical interventions (Sela and Bab 2012). Depending on the size of the defects, they are categorised as small and large segmental bone defects (discussed in the next section).

2.3 Large segmental bone defects and causes

Bone repair and regeneration following traumatic defects or pathological diseases include a series of morphological, immunological, and biomechanical activities that ultimately result in the restoration of bone structure. Despite the significant medical and economic consequences of such injuries, there is still a large burden of diseases concerned with their treatment. Also, despite the significance of evidence-based decision-making, there is still a fundamental disagreement on definitions, accurate models, and appropriate methodologies aimed at the clinical treatments of segmental bone defect. The management of complicated fractures or several bone deformities resulting from trauma, infection, congenital defects, osseous reconstruction, and tumour excision has improved considerably as clinical procedures, implant models, and peri-operative treatments have improved (Molina et al. 2014, Lasanianos et al. 2010, Vidal et al. 2020). If required and performed, reconstructive surgery must assist rapid healing and is classified according to the type of the bone defects being treated. Specific precautions must be considered if these defects are large- segmental bone defects of the upper or lower limbs, based on the defect level, cause, or any associated comorbidity.

2.3.1 Definition

Defining "Critical" in Bone Defect Size

Segmental bone defects (SBD) also commonly known as critical size defect (CSD) have no standard definition. CSD are defined (according to various animal experiments) as the smallest bone gap in a specific bone and type of animal which can never regenerate naturally throughout the animal's lifespan." (Rimondini et al. 2005, Gugala and Gogolewski 1999). They are also known as segmental bone defects when length of damaged bone exceeds 2 to 2.5 times its diameter (Gugala et al. 2007, Lindsey et al. 2006). Figure 2.10 shows the types of long bone defects.

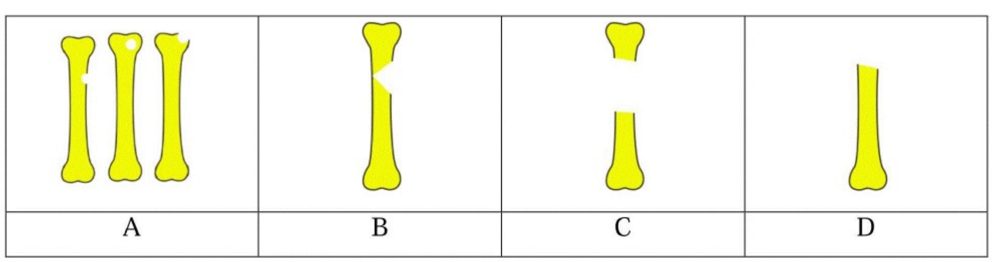

Figure 2.10: Categories of segmental bone defects. A: Limited defect; B: Bone fragments have contact; C: Bone fragments have no contact (segmental defect); D: Complete articular defect. (Solomin and Slongo 2016).

The Orthopaedic Trauma Association defines a segmental bone defect as one that is more than 1-2 cm long and has a circumferential bone loss of more than 50%. The exact bone length or volume that constitutes a CSD is not clearly specified in the survey of Orthopaedic Trauma Association that utilised bone graft technique for "critical-sized" bone defect (Obremskey et al. 2014). A defect size above 2 cm and a gap exceeding 50% of the bone diameter are proposed in the literature as general parameters (Keating et al. 2005, Sanders et al. 2014).

Consequently, a bone defect may be classified as critical based on various factors other than its length. Anatomical site (endosteal/perioseal/condylar), surrounding tissue environment and associated biomechanical challenges of the affected bone, patient's age, physiological issues, and relevant co-morbidities can all influence the process of bone repair (Lasanianos et al. 2008, Martinez et al. 2008, Oh et al. 2008, Talbot et al. 2008). Figure 2.11 shows the classification of bone defects on basis of defect size and site (Solomin and Slongo 2016). All such factors make it difficult to establish an overall categorization strategy for segmental long bone defects.

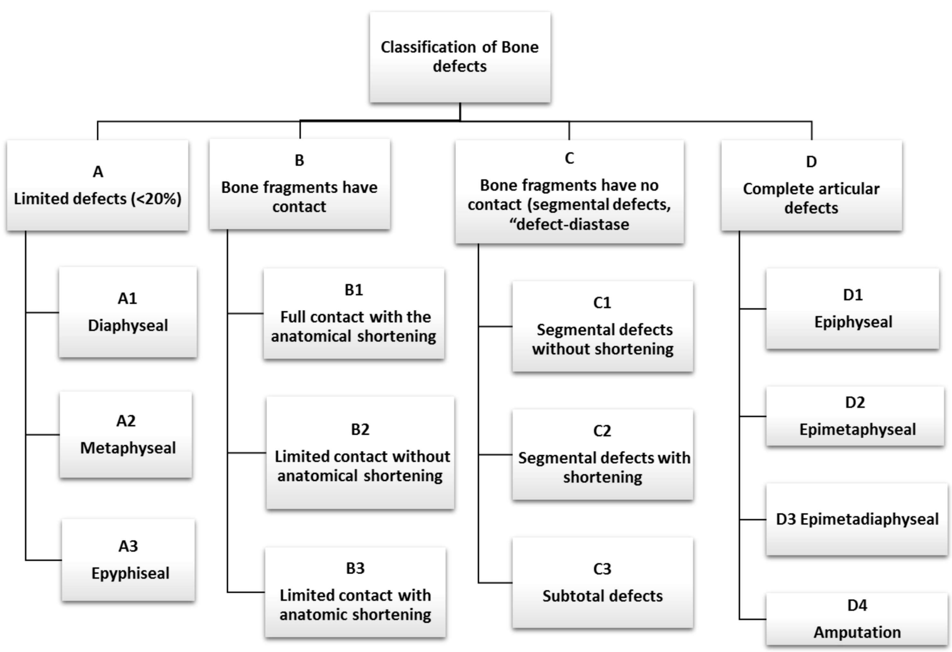

Figure 2.11: Classification of bone defects on the basis of defect site and size (Solomin and Slongo 2016).

2.3.2 Size matters:

When considering the efficacy of SBD of any bone such as femur or tibia, the impact of anatomic site is apparent. The environment of soft tissue surrounding femoral defects is generally favourable, and spontaneous repair of these defects ranging from 6 to15 cm in length is mentioned in literature (Hinsche et al. 2003). When the size of defect is above 2 cm and exceeds 50% of cortical diameter, inappropriate results with absence of spontaneous repair have been observed (Blick et al. 1989, Court-Brown et al. 1991). Defects ranging from 1 to 2.5 cm in length cannot be considered as critical and are developed unequally, since almost 50 % of them may recover completely.

Although some studies suggest that for a bone defect below the size of 6 cm may not necessarily require surgical interventions. The problem emerges when the bone gap is in 8 and 12 cm range and is classified as critical above 12 cm (Obremskey et al. 2014). However, the management of segmental or critical size bone defects is not well established.

2.3.3 Causes:

A segmental bone defect (SBD) is presently an exigent and expensive issue in the orthopaedic field. The most common factors leading to segmental defects include high intensity trauma, pathophysiological conditions like population aging, infections, tumour or osteomyelitis excision, congenital disorders, and revision surgery (Figure 2.12) (Keating et al. 2005).

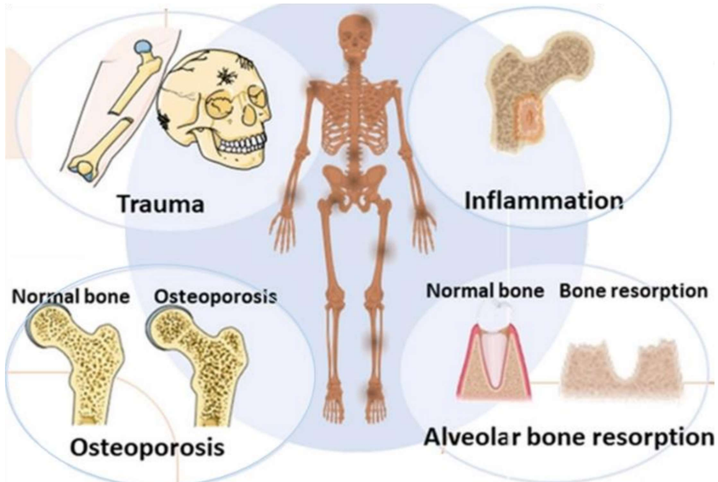

Figure 2.12: Causes of Bone loss. (Zhou et al. 2021)

An inappropriate wound condition, poor surgical technique, or biomechanical imbalance, on the other hand, might result in the development of major defects having limited ability for regeneration (Perry 1999). Owing to limb length mismatch and lengthy treatment procedures, such defects possess a substantial clinical, socioeconomic, and scientific burden, and can significantly affect the quality of patients' life (DeCoster et al. 2004, Clements et al. 2008).

2.3.4 Reconstruction alternatives of SBD:

In most conditions of trauma or excision owing to malignant, diseased, or defective bone tissue, SBD presents a significant reconstruction challenge. Although, there is no established standard treatment approach defined for bone defect reconstruction due to a wide range of risk factors and complications of pathological conditions associated with it.

Some frequently used reconstruction alternatives for segmental bone defects include bone graft methods, use of synthetic material, Masquelet's induced membrane technique, Ilizarov method, and the use of metallic bone implants. These are shown in Figure 2.13 and briefly described in this section.

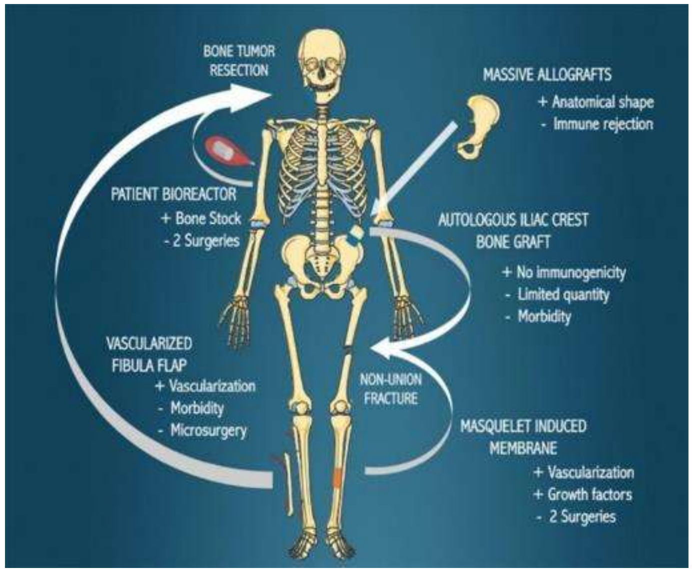

Figure 2.13: Present biological approaches for bone reconstruction. Bone defects caused by tumour excision or non-union fractures are being addressed using numerous ways mentioned, and merits/demerits of each treatment is highlighted. (Vidal et al. 2020)

Bone Grafts

Bone grafting is still the most often used procedure for bone defect restoration with an objective to enhance the healing procedure (Albrektsson and Johansson 2001). Based on the tissue source, they can be classified as autologous bone grafts, allografts, and xenografts, along with biological and synthetic biomaterials (Brydone et al. 2010).

Autografts

Autologous grafting of bone is the standard clinical reconstructive approach that involves extracting bone tissues by a functional donor location then transferring those to recipient's damaged area (Sanan and Haines 1997). The primary disadvantages include discomfort, haemorrhage, probable internal lesions at the donor site, complications at the implant site, and prolonged operating time due to the separate surgical locations. Additional problem is the inability to get significant quantities of bone graft for large segmental defect restoration (Oryan et al. 2013).

Allografts

Allograft bone is extracted either via alive donors undergoing reconstructive surgery or by skeletal remains followed by preserving, preparing, and implanting them inside the patient (Keating and McQueen 2001). Allografts have replaced autografts in the treatment of large segmental defects due to their imperfections. The instant accessibility in various dimensions and types is one of the principal benefit of allografts. Allografts, on the other hand, have varied tissue adhesion and proliferation abilities but a lesser differentiation capability in contrast to autograft (Coquelin et al., 2012). Also, the risk of immunological intolerance as well as infections are additional drawbacks (Aro and Aho 1993).

Xenografts

The most frequently implemented xenografts have been obtained from cow, pigs, and even coral source collected out of several organisms and implanted for the purpose of bone recovery. Quick accessibility, optimal porosity enabling tissue regeneration, as well as biomechanical stability similar as natural bone are the main benefits (Bansal et al. 2009). One of their significant drawback includes the possibility of infections and immunological intolerance. Also, there are ethical and theological issues with xenografts.

Synthetic Biomaterials

Tissue engineering employs the biomaterials in conjunction to biological components for enhancing the functioning of living organisms. A variety of biomaterials have been used to cure bone abnormalities like calcium phosphate (CaP) ceramics. calcium phosphate cement (CPC), and bioactive glass (bio glass). For the treatment of minor segmental defects, synthetic implant replacements have been a viable option against bone grafts. Bone substitutes, although, cannot be the ideal solution because of the inadequate ability to sustain the weight of body as well as poor neovascularization (Stanovici et al. 2016).

Masquelet Induced Membrane Technique

The Masquelet technique, or induced membrane approach, is a surgical process carried out in two steps where at first, a cemented polymethyl methacrylate (PMMA) implant is inserted and a pseudo synovial membrane is created, followed by the extraction of the cemented implant after 6 to 8 weeks is replaced by an autograft thereby retaining the induced membrane. The promising approach is appropriate for youth and adolescents with severe and long term defects ranging 4 to 25 cm at various anatomical locations (Masquelet et al. 2000). Pathogenic issues, operative treatment failure at any step, revision surgery, and acute implant fatigue are major concerns.

Ilizarov Method

This method is used to treat multiple disorders in a patient containing defects like osteomyelitis, communal fractures, or non-union infections (Ilizarov et al. 1990). An external ring fixation together with corticotomy are used in this method to improve bone stability for fast recovery. This method also facilitates the correction of an axis defect and limb lengthening, although, the disadvantages include delayed recovery with long term hospital stay causing inconvenience to patients, and even osteomyelitis consequences.

Metallic Bone Implants

Metal implants, rather than re-growing the bone tissue, replace the defected potion of bone. The material composition of these implants has undergone substantial modification since their conception, assuring protection against corrosion, eliminating implant failure by improving fixation and stability to promote bone ingrowth and repair. Novel modular prostheses enable the combination of multiple materials for facilitating custom-made or patient-specific designs to treat large segmental bone defects (Hattori et al. 2011). Metallic implants used for different anatomical locations are shown in Figure 2.14. (Wu et al. 2021).

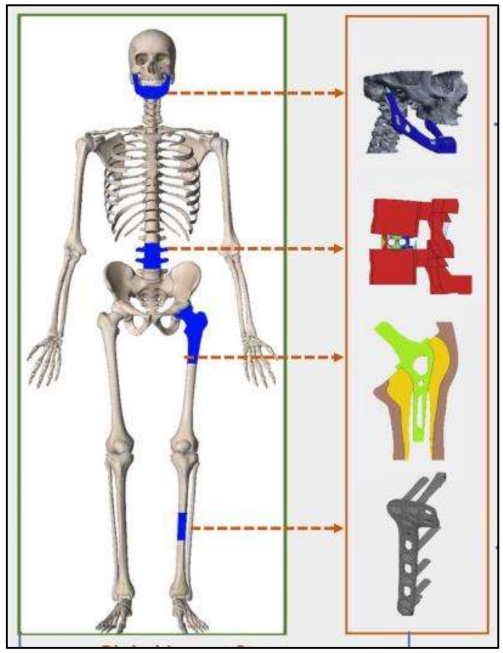

Figure 2.14: Metal implants for orthopaedic applications. (Wu et al. 2021).

Intercalary reconstruction can be replaced by segmental prosthesis (Figure 2.15). They provide instant stabilization, quick recovery with fast load carrying capacity (Ahlmann et al. 2006). Because of the significant danger concerning implant failure, it is recommended in patients with malignancies or bone tumours having reduced longevity of life (Panagopoulos et al. 2017, Zheng et al. 2019). As a result, the preferred patients essentially requiring this approach include older adults needing faster recovery where early load bearing and immediate stability are a priority above longevity.

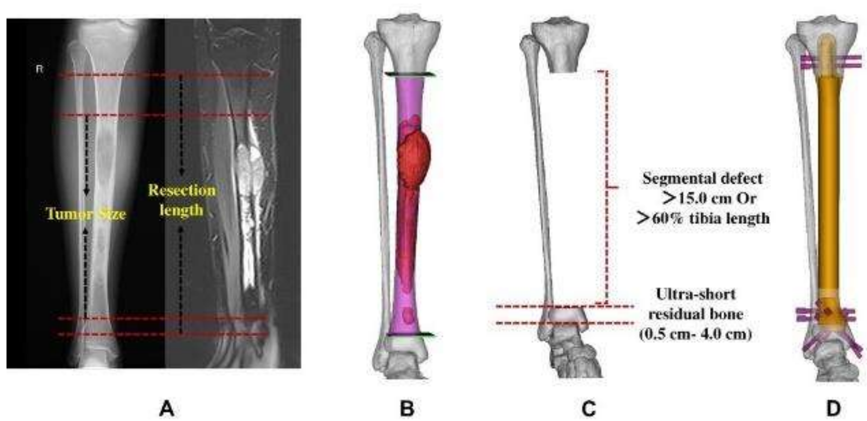

Figure 2.15: Intercalary reconstruction using segmental metal prosthesis (Zhao et al. 2020).

The major problems involved after metallic implantation include mechanical and non-mechanical complexities and are discussed in the next section. Although implants with silver coatings, antibacterial medications, combined with rigorous clinical methods may prevent such issues, non-mechanical consequences still remain a greatest hazard while treating a massive bone defect with solid metal prostheses.

Large segmental bone defects, therefore, can be treated using a prosthesis that maintains good weight carrying capacity and simultaneously enhancing efficient reconstruction, contributing towards the development of more stable and durable implant or scaffold structure (Figure 2.16).

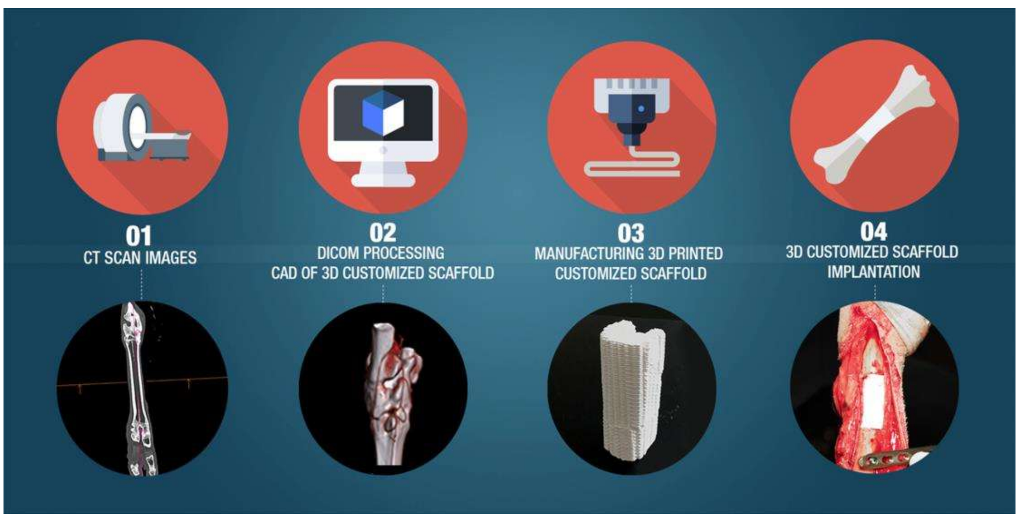

Figure 2.16: Processes involved in the manufacture of custom-made bone implants. (1) Bone CT scans are obtained for the patient. (2) Computer-aided software allows CT scans to be processed for (3) 3D printing customized constructs for (4) restoration of bone defects. In the bottom half, a genuine significant bone defect restoration process in metatarsal bone model of sheep is illustrated. (Vidal et al. 2020)

2.4 Post-operative complications associated with implants

Several mechanical and non-mechanical complications are associated with metal implants. Stress shielding, implant weakening and fatigue, lack of cell adhesion, as well as no possibility of bone ingrowth and nutrient transportation are all mechanical issues associated with the conventional solid implant design, reported in the literature (Bugbee et al. 1997, Sumner 2015). Besides this, infections, recurrence of cancer cells, or even tissue repair limitations are examples of non-mechanical consequences.

2.4.1 Mechanical Complications

Implant failure occurs due to different biomechanical issues like fatigue failure, stress shielding, failed ingrowth, particulate reaction, and destructive wear (Cowin and Telega 2003). In vivo and in vitro examinations revealed that the bone loss caused by the stress shielding effect and failure at the interface of bone and implant due to improper interfacial conditions may contribute to the aseptic loosening of implant.

2.4.1.1 Stress shielding

As discussed in previous section, bone resorption can be caused by changes in physical activity (an unhealthy person has fragile bones) and also by the placement of stiffer metal implants that lower the stress sustained by the bone. This results in the phenomenon called stress shielding. Since metal implants are designed to be durable for years, the stress absorbed by the surrounding bone decreases. As a result, the stress applied on the bone is comparatively less, resulting in bone remodelling (Goodship and Cunningham 2001, Shanbhag and Rubash JJJ 2005). Unfortunately, it diminishes the density of bone, resulting in bone weakening. This causes implant displacement, dislocation, and can lead to ultimate failure (Shanbhag and Rubash JJJ 2005, Sumner 2015). Comprehensive theoretical and experimental research is reported in the literature on the stress shielding of using solid implants (Goodship and Cunningham JL 2001, Shanbhag and Rubash JJJ 2005, Sumner 2015, Glassman et al. 2006, Huiskes et al. 1992, Cristofolini 1997). Total hip replacement being one of the frequently reported implant reconstructions, report highest stress shielding and bone resorption due to the presence of a solid stem that are evident in the proximal region of the femur (Figure 2.17).

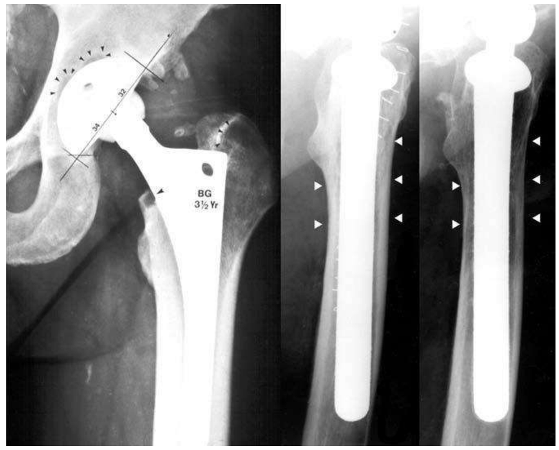

Figure 2.17: Stress shielding in the proximal part of the femur due to bone-implant stiffness mismatch. Radiography compares the bone after 5 years of implantation (locations are highlighted) (Shanbhag and Rubash JJJ 2005).

2.4.1.2 Interface failure

There are many reported cases of implant subsidence due to large stresses at the bone implant interface. In the immediate postoperative situations, increased stresses at interface cause high level of pain, which results in micro movement that would inhibit the bone ingrowth in implants leading to decreased interface bond and ultimate failure. In addition, both the mechanical causes of failure are also dependent on mechanical properties and shape (Kuiper and Huiskes 1992, Kuiper and Huiskes 1997).

2.4.2 Drawbacks of solid implants:

Conventional orthopaedic implants are usually made of solid metals. They possess substantially greater stiffness value as compared to natural bone. Substantial difference in the morphological characteristics of bones and implants causes a variety of negative consequences. Stress shielding is one such factor experienced by neighbouring bones due to inequalities of elastic modulus, which causes very low stresses to be experienced by the neighbouring bone (Bansiddhi and Dunand 2014), resulting in its degradation, as well as serious issues like implant loosening (Ryan et al. 2006), instability and durability (Harrysson et al. 2008). Also, there is no possibility of bone ingrowth and tissue proliferation (Wang et al. 2008, Ryan et al. 2008). Main drawback of using solid metal implant (usually made of Ti alloys) for reconstructing cancellous deformities is its elastic modulus greater than 110 GPa, which is significantly higher in comparison to cancellous bone and cortical bone with an elastic modulus of ranges from 0.02 to 0.5 GPa and 3 to 30 GPa, respectively. This significant difference leads to lower stress transfer to surrounding bones and leads to bone loss at implant interface. [Sumner et al. 1998, Dhert et al. 1992). However, implementing low stiffness materials reduces bone resorption but enhances the bone-implant interface tension. (Zhang et al. 2021). This results in contact failure and subsequent implant loosening (Sumner 2015, Huiskes et al. 1992).

Minimising the stiffness gap between bone and implant, stress shielding can be reduced. Besides, the loading direction also has a significant impact on stress shielding [Shanbhag and Rubash JJJ 2005, Sumner 2015). The quantity of bone degradation have a dependency on whether the implant is cemented or non-cemented. The cemented implant aids in the uniform distribution of load which decreases stress shielding but using cement have other associated serious complications (Park et al. 2006).

2.4.3 Current approaches to avoid stress shielding:

The major approach for reducing the effect of stress shielding is by minimising the stiffness of implants. Techniques involved to accomplish this approach include: Improvement in implant geometry and design parameters, adjustment in material characteristics, and perhaps a combined effect of both the mentioned approaches. Structural modifications are proposed for reducing the effect of stress shielding depending on the type and location of treatment.

Structural changes incorporate implant's cross-sectional modifications and porosity (Wycisk et al. 2013). Solid implants are being incorporated with porous geometry to obtain complete porous scaffold structures (Figure 2.18). The fundamental concept is to improve bone ingrowth, assure appropriate stress transfer as well as minimize the stiffness by modifying its structure either by employing porous coatings on the surface of implant or even by developing a completely porous implant.

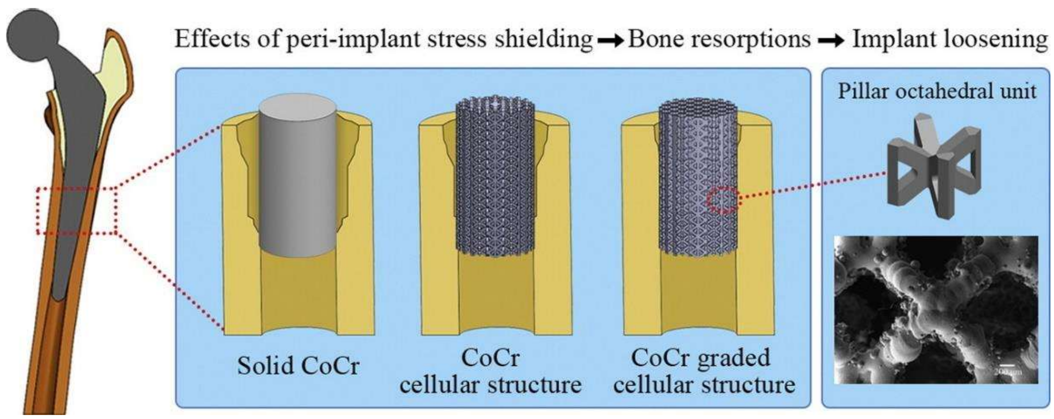

Figure 2.18: A portion of solid hip implant is replaced with porous structure to avoid stress shielding and it's after effects (Limmahakhun et al. 2017).

Therefore, developing an appropriate customised patient specific implant (PSI) is a complex procedure as it is essential to maintain a balance between the stress shielding effect and the associated contact stresses (Huiskes et al. 1992, Huiskes et al. 1989, Kuiper and Huiskes 1997). A non-homogeneous implant can be a suitable solution for balancing stress shielding and interfacial stress caused by implantation (Kuiper and Huiskes 1997). Depending on the application, non-homogeneous materials possess a change in their characteristics from one area to the other continuously. Bone is one such example of a naturally occurring non-homogeneous material. The bone parameters change continually from low stiffness cancellous bone at the interior to high stiffness cortical bone at the exterior. As a result, structural modifications in non-homogenous materials have resulted in the introduction of totally porous implants with controlled relative density (Epinette and Manley 2004, Levine 2008, Moussa et al. 2018).

2.5 Need of Porous Structures for the Treatment of LSBD

As mentioned earlier, solid implants lead to stress shielding and hence bone loss while using a compliant design leads to high stresses at the bone-implant interface. The above-mentioned disadvantages led to the idea of fully porous implants instead of just a porous coating [Zanini et al. 2018, Karamooz et al. 2016, Kadkhodapour et al. 2015). Some important properties of an ideal metal bone implant include (Hollister 2009):

(i) biocompatibility, enhancing implant stability;

(ii) bone mimicking properties of implants to avoid stress shielding and failure;

(iii) appropriate porosity ensuring bone ingrowth and permeability to nutrient and blood transport;

(iv) optimal structural morphology for cell adhesion, proliferation, and differentiation which cannot be achieved by fabrication of implants with conventional porosities introduction methods (Aust et al. 2006).

2.5.1 Introduction to Porous structures

Porous (cellular) structures are classified as materials that consists of two phases: a solid phase and an empty/fluid phase. Porous structures are composed of a series of interconnecting plates and solid strut that defines the cell's face and edge. Nature has a wide range of porous structures, including wood, cork, bone, and coral (Tan et al. 2017, Nazir et al. 2019). Three elements primarily determine the characteristics of porous materials which include the composition and properties of materials used (Metals, polymers, and ceramics), topological specifications (wall thickness, size, and shape of unit cells), the relative density or porosity (Ashby 2006).

The edge or wall thickness corresponding to the unit cell ranges from micrometres to millimetres. The porous solids may be considered as structures and materials simultaneously due to the availability of unit cells in millimetre or micrometre ranges (Ashby 2006). As a result, both material and structural factors affect the mechanical behaviour of porous solids, including elastic modulus and compressive strength (Bauer et al. 2014).

The mechanical performance of porous materials are commonly predicted by compressive stress-strain plots. Figure 2.19 shows the basic stress-strain graph of porous materials. Elastic region, plastic deformation, and fracturing are the three domains of the stress-strain curve. The material response is linear in the elastic domain; although, Gibson et al. proposed the measurement of modulus of elasticity (Young's modulus) of porous materials upon unloading (Gibson and Ashby 1997).

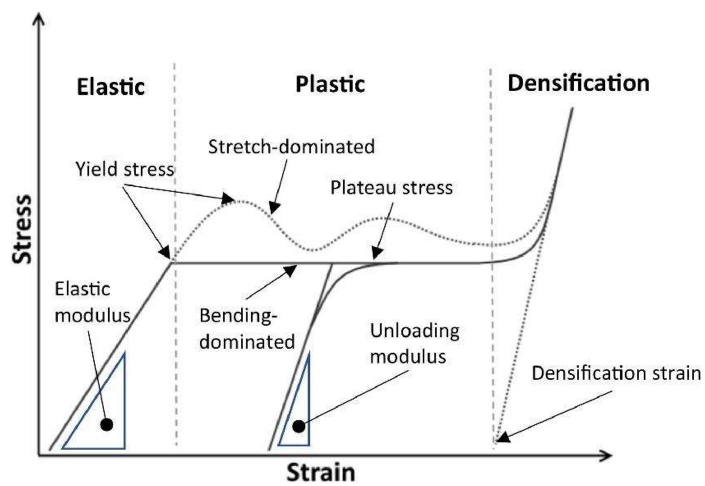

Figure 2.19: Illustration of compressive stress-strain curve for porous structures (Maconachie et al. 2019).

The mechanical properties of porous structures get significantly influenced by the porosity of material. Hence, developing porous scaffolds with adequate mechanical characteristics is the main challenge in porous bio-implant research, presently. To construct bone-mimicking scaffolds with better bone regeneration abilities, control over porosities, size of pores, surface area, and permeability, together with the manipulation of strength and stiffness is essential

(Figure 2.20). Parameters like pore shape, pore size, strut size, and porosity substantially influence the mechanical and biological characteristics of load-bearing implants (Zaharin et al. 2018, Kadkhodapour et al. 2015, Wieding et al. 2012).

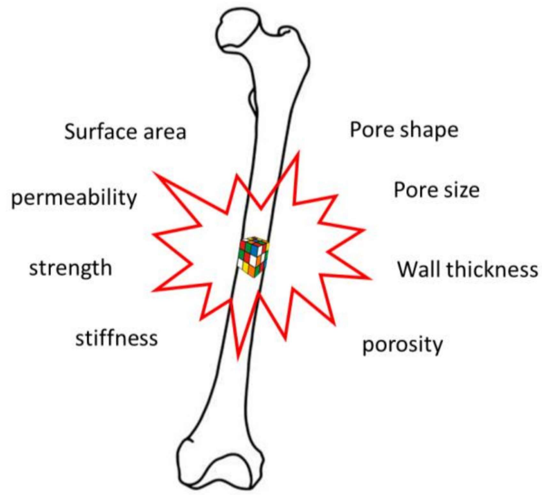

Figure 2.20: Morphological and mechanical parameters affecting porous implants.

The relationship between morphology and material properties must be studied to achieve an optimum balance between mechanical strength and biological properties.

Optimization of pore size and porosity has been the major concern of researchers as it directly affects osseous regeneration (Cai et al. 2019, O'Brien et al. 2007). An appropriate balance between pore size, strut size, and porosity ensures better bone ingrowth, cell adherence, gaseous diffusion, nutrients, and fluid transport (Wang et al. 2017, Rahbari et al. 2017). The pore shape governs the elementary structure of porous scaffolds and has a direct impact on tissue behaviour to promote bone regeneration (Van Bael et al. 2012). However, the most essential challenge to resolve is the relationship between porosity and mechanical characteristics of porous scaffolds for orthopaedic applications.

Relative density is another factor that has a direct impact on mechanical behaviour, although modifications in geometry (open or closed type of pore shape) can solve this problem depending on whether the cell is closed or open. Similarly, type of materials used also influence the mechanical performance of structure.

Porous materials appeal because they offer a diverse combination of structural and mechanical characteristics. Lightweight along with higher stiffness or low thermal conductivity combined with strong energy absorption characteristics are some typical examples [Li et al. 2014). Their application areas can be categorised as: Structural and functional. Biomedical implants, load-bearing elements, and energy absorbers are examples of structural applications. Acoustic treatments, filters, and heat diffusers are examples of functional uses in other engineering applications areas. Banhart et al. discussed such applications by graphical representations (Figure 2.21) rating these in terms of the degree of "openness in porosity." (Banhart 2001).

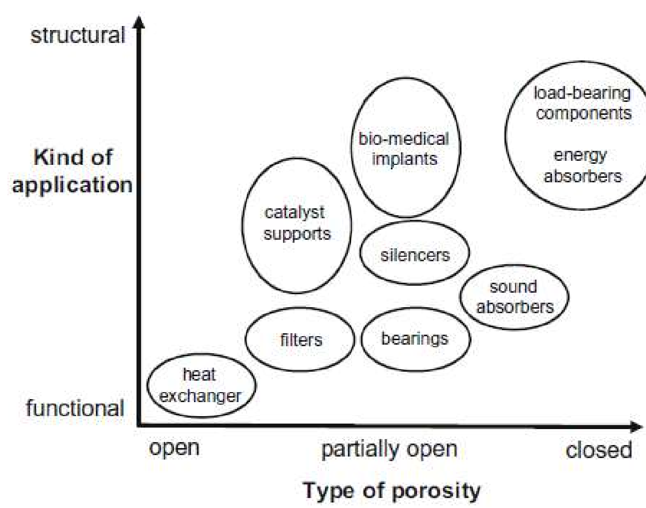

Figure 2.21: Applications for porous materials (Banhart 2001).

This study will only consider geometries associated to porous structures with open pores, as they enable tissue ingrowth and nutrient transport within the implant. Wide range of structural configurations are available in literature to develop open porous structures. To resemble the physiological characteristics of natural bone, the geometry of these structures are modified to obtain variations in porosities, sizes of pores, diameter of struts, shapes and orientations of unit cell. Wide range of porous structures can be manufactured using additive manufacturing (3D printing) technology (Michielsen and Stavenga 2008, Pouya et al. 2016). A range of these structures are obtained by effectively modifying porosity and shape of pores to develop a potential structure that promotes tissue regeneration. Hence, certain criteria must be followed to obtain a variation in the structural properties which generally include, the strength and stiffness to reduce as porosity increases which eventually improves the material permeability.

2.5.2 Advantages of Porous structures in implant applications

Due to the disadvantages imposed by solid metal implants, the concept of porous coating on the surface of solid implants were introduced over decades. Previous researches report the use of porous coatings to reduce the effect of stress shielding, also helps in better fixation and support bone in growth in implants [Gibson et al. 2010, Ryan et al. 2006, Cheryl et al. 2005). Although, these have some drawbacks such as introduction of notches on the metal substrate during the coating process which acts as stress concentration points. This can lead to a decrease in implant's fatigue strength, which is considered during the design phase. Next, the coating on the metal substrate can detach overtime if not considered. The above-mentioned disadvantages led to the idea of fully porous implants instead of just a porous coating (Murr et al. 2010).

Hence, to resolve all such issues, the researchers are continuously struggling to develop the most compatible porous metal implants rather than a solid one. Porous implants are recommended for their lighter configurations, suitable load bearing and stress distribution abilities, better fixation, permeable properties allowing nutrient exchange, as well as potential for tissue ingrowth and regeneration (Mauffrey et al. 2015, Qin et al. 2017, Matassi et al. 2013, Dabrowski et al. 2010). Another important benefit of adopting porous structures lies in its ability to imitate the structural, mechanical, and biological qualities of natural bone, that remains unexplored in solid constructs (Ponader et al. 2010, Palmquist et al. 2013).

Porous implants (scaffolds) are built particularly to resemble bone and are also lightweight constructions when compared to traditional implants. These structures are effectively implanted at the defect site with a purpose of obtaining desired stiffness. Porosity (presence of holes) can be observed in several organic materials including bone. The presence of pores renders the material to be lighter in weight and provides permeability that facilitates nutrient transport across the pores. The pores assist in the remodelling of bone by varying its density according to applied mechanical loads. Researchers have struggled over decades to develop suitable products containing identical characteristic that mimic bone. Latest researches report that the conventional solid metallic implants are now being incorporated with the micro-structural pores rather their geometry and orientation which cannot be controlled precisely (Figure 2.22).

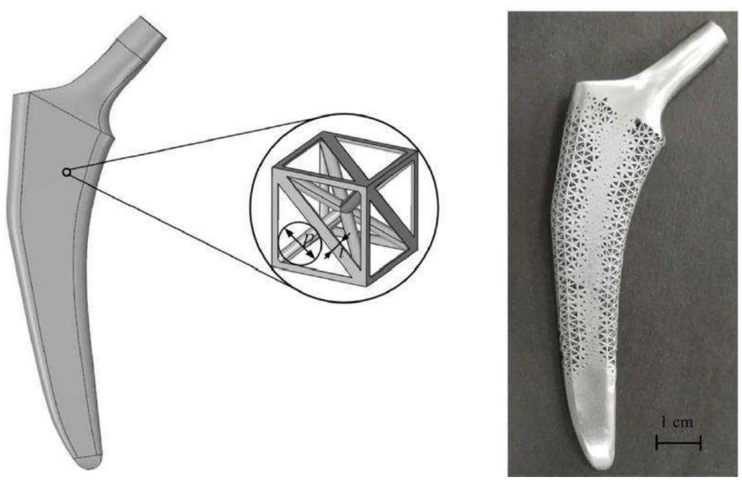

Figure 2.22: Fully porous stem developed by a tetrahedron unit cell. (Moussa et al. 2018).

These novel optimized designs are termed as porous scaffolds that possess the ability to customize structural-material relationship for its improved efficiency. Modifications in the structure allows stiffness to be obtained in multiple orientations. Also, alterations in the pore geometry, stiffness, as well as changing the pore direction at the areas carrying load regulates the stiffness. As per the research in this field, this technology paves a way for the development of implants made of a variety of material compositions since geometry-material relationship enables the manufacturers to improve its efficiency.

Literature reports that the three-dimensional porous scaffolds are a versatile solution for SBD as they can be used for osseous reconstruction to reinstate the functionality of bone (Yánez et al. 2018).

2.5.3 Types of porous structures

Porous materials vary in shape and size, and can be categorised as shown in Figure 2.23 below:

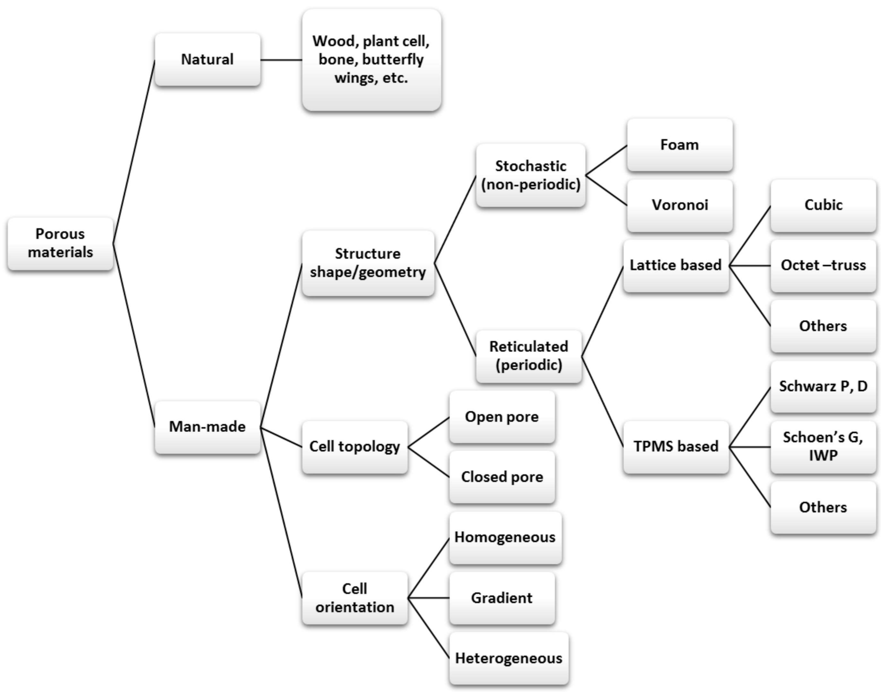

Figure 2.23: Classification of porous materials based on multiple factors.

Natural and man-made: Porous structures have been first identified in naturally existing materials including trabecular bone, butterfly wings, woods, etc., before being manufactured as artificial materials. Researchers have developed strategies to reproduce the naturally existing porous structures that possess remarkable physical and mechanical capabilities. Advancements in fabrication technology have improved customization in fabrication approaches which promotes researches towards topological optimization techniques aimed at determining desired shape for a specific set of constraints.

• ***Closed and open pore:*** Porous structures are called open porous materials if they consist of solid edges only. For closed porous materials, there exists both the solid edges and faces.

• ***Stochastic (non-periodic or irregular) and reticulated (periodic or regular) porous structures:***

Generally, stochastic structures contain irregular distribution of open or closed pores. For example, foam structures constructed by a random orientation of struts and faces that result in the development of open or closed type of foam structures which are typically heterogeneous, making the foam stronger at certain locations but weaker at other sites. These weaker sections substantially reduce mechanical properties (Murr et al. 2010). However, novel voronoi based structures have shown improved results to improve the mechanical properties of stochastic porous structures (Wang et al. 2018). Figure 2.24 shows stochastic porous scaffolds. Banhart et al. (Banhart 2001) presented a very comprehensive study on stochastic porous metals, describing the manufacture, analysis, and use of such materials, for a detailed evaluation.

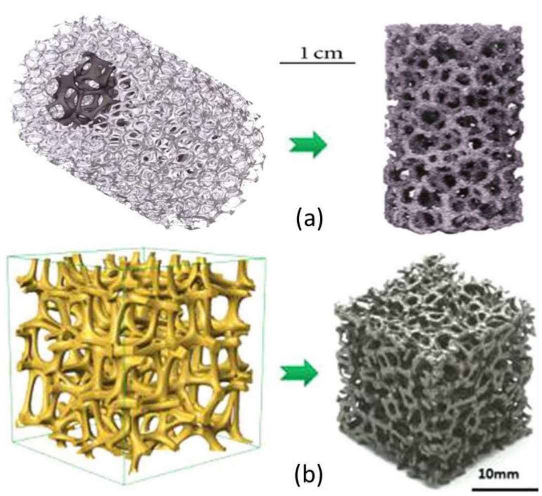

Figure 2.24: Stochastic porous scaffolds (Murr et al. 2012). a) Foam based scaffold structure and b)Voronoi based scaffold structure Reprinted (adapted) with permission from (Wang et al. 2018).

Reticulated (or periodic) structures are frequently available and are composed of repeated unit cells. These exhibit exceptional mechanical characteristics, including significant stiffness and strength. Main benefits of employing periodic lattices over stochastic structures includes their ability to be customised to obtain desired structures for suitable applications. When compared to stochastic constructions, the structural properties in periodic structures may be conveniently adjusted to exhibit higher weight bearing capabilities and surface area (Williams et al. 2011). This property allows reticulated porous designs being incorporated in metals, resulting in superior multipurpose behaviour for components utilised in aerospace, automotive, as well as clinical technologies (Zhou et al. 2004, Amerinatanzi et al. 2018).

The periodic porous structures can further be categorised as lattice based porous structures and triply periodic minimal surface (TPMS) based porous structures.

Lattice-based porous structures:

The lattice structures belong to the group of porous materials, therefore are synonymously referenced in literature. Lattice structures contain open pores that are periodically arranged by the repetition of unit cells in a regular pattern. This periodical organisation of unit cell is known as reticulated which is usually referred as lattice structure. Failure of such lattice structures is indicated by the stretching and bending deformations. Because of the improved mechanical characteristics obtained for reticulated structures, they are preferred over stochastic models (Mahmoud and Elbestawi 2017). Unit cell structure and topology influence the mechanical characteristics and are categorised depending on their formation or deformation characteristics (Tan et al.2015).

Selecting a suitable unit cell structure from a vast library is one approach of constructing a 3D printed porous scaffold. Several alternative unit cell structures were constructed and investigated so far, ranging from the simplest cube or triangulated prisms to a complicated octagonal prism or rhombic dodecahedron . These include:

- Honeycomb structures: that are widely recognized for providing anisotropic mechanical characteristics or are available as sandwich structures so as to sustain any type of load (Wang et al. 2021, Zhang et al. 2015).
- 3D strut-based lattice structures: like BCC, BCC-Z, FCC, FCC-Z (Ashby and Gibson 1997), Octet-truss, Kelvin lattices (Deshpande et al. 2001, Wang et al. 2003, Hyun et al. 2003). Strut-based lattices are often prioritised because of the simple construction and configuration , however can be referred for research in topology optimization applications (Xiao et al. 2018, Challis et al. 2010).

Triply periodic minimal surface (TPMS) based porous structures:

Periodic minimal surface has been widely explored as hyperbolic surface. Minimal surface shows periodicity in three different directions, hence, is called Triply Periodic Minimal Surface (TPMS) (Qi and Wang, 2009; Jung et al, 2007; Wang, 2007; Gandy et al, 2001; Wohlgemuth et al, 2001). TPMS can be considered as biomimetic as they resemble various natural structures including liquid crystal of lyotrope, crystalline structure of sodalite-zeolite, di-block copolymer, hyperbolic membrane in plants, echinoderm skeletal plate, cubosomal structures, along with several cellular membrane structures (Larsson et al, 2003; Hyde, 1996; Andersson, 1983; Scriven, 1976). TPMS have been widely used for enhancing bone ingrowth in porous scaffolds [Zadpoor 2015, Fantini et al. 2017, Bobbert et al. 2017). Currently, these structures have gained much importance. In comparison with traditional strut-based unit-cells, TPMS represent rather complicated geometry, however with rapid advancements in 3D printing technology, manufacturing of TPMS based structures is easily accomplished. TPMS topologies are categorized as R3, also called rank-3 translation lattice that possess symmetric-crystalline geometry. Hermann Schwarz reported Schwarz to be the first case of TPMS in 1865 (Schwarz, 1972). After which, 12 additional TPMS were reported by Alan Schoen based (Schoen 1970). Despite the fact that Schoen's constructs became well-known, they were not mathematical validated until H. Karcher in 1989 confirmed their presence (Karcher 1989). Several additional structures were discovered with complementary surfaces. Weierstrass gave relatively simple illustrations, however those approaches were depicted using Discrete differential geometry (Karcher and Polthier 1996). Some of the commonly used periodic (lattice and TPMS) structures reported in literature for developing porous implants are shown in Figure 2.25.

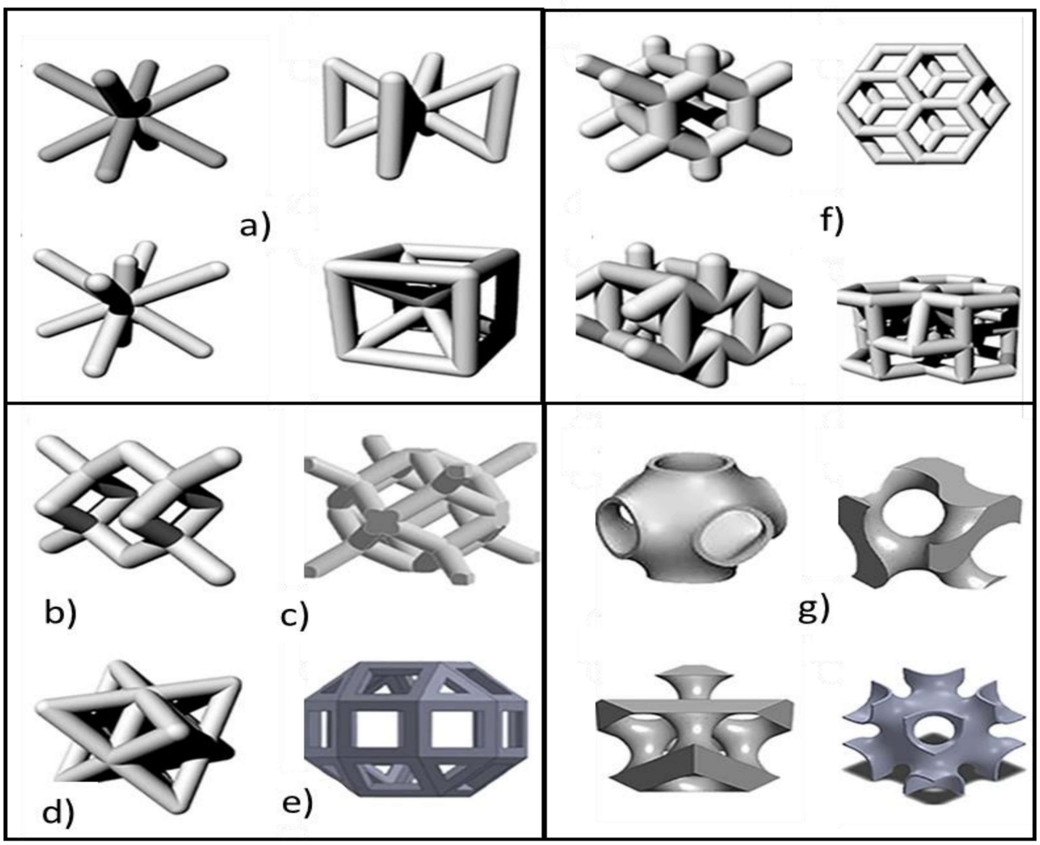

Figure 2.25: Different unit cells of periodic porous structures showing a) BCC and its modified units, b) strut-based diamond unit cell, c) octet strut d) rhombic dodecahedron strut, e) rhombic cube octahedron strut, f) honeycomb unit cells, and g) TPMS based unit cells (Chen et al. 2020).

2.6 Triply periodic minimal surfaces (TPMS)

2.6.1 What are TPMS structures

TPMS are considered to be originated from a class of minimal surfaces. These are nature-inspired materials that are found to exist naturally in soap films (Schoen 1970) and butterfly wings of Cyanophrys, specifically Teinopalpus imperialis and Parides sesostris (Michielsen et al. 2008) that consist of many differently orientated, geometrical structures (Figure 2.26) (Corkery and Tyrode 2017).

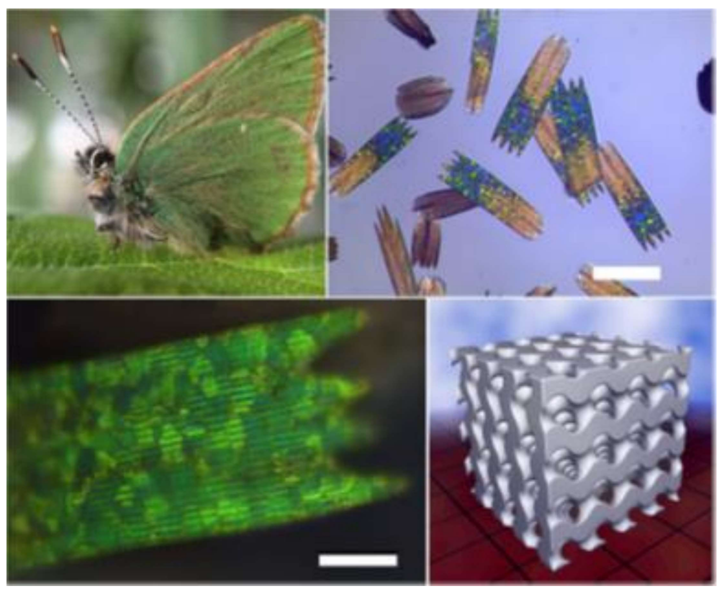

Figure 2.26: Nature inspired TPMS gyroid structure obtained from a) butterfly wings (Callophrys rubi), b) microscopic image of scales of C. rubi, c) magnified image of scales, d) CAD model of gyroid structure inspired from the wings of C. rubi. (Corkery and Tyrode 2017).

Mathematically, minimal surfaces are those surfaces which minimize the area locally or possess mean curvature equal to zero lying on each face of the surface (Figure 2.27). Hence, they can be simultaneously convex as well as concave throughout the surface giving them a saddle shape resembling a saddle or a hyperbolic curve.

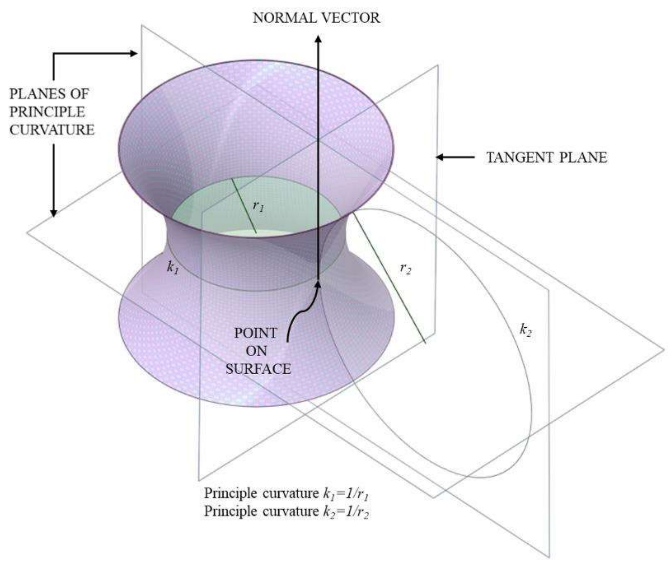

Figure 2.27: Illustration of the surface with constant mean curvature, representing the maximum and minimum curvatures (k_1 *and* k_2) at a point on the surface

These are termed as "minimal surface" as they are evolved from surfaces that reduced overall surface area. Wired frames dipped inside soapy solutions generate soap films, which have minimal surfaces with wire frames as their boundary, and physical models of these surfaces may be created by this concept.

Minimal surface containing crystallographic structures with repeated geometries in three dimension, or being triply periodic, are extremely interesting. These triply periodic minimal surface include three lattice vectors, indicating their stability in three-different directions. These are commonly referred as triply periodic minimum surface (TPMS).

TPMS can be represented by a series of equations. Figure 2.28 shows that they have a porous structure that is smooth and continuous, having no jagged corners or edges, and divide the area into two or more interconnected, non-superimposed, infinite regions that can be replicated over three perpendicular directions (Góźdź and Hołyst 1996).

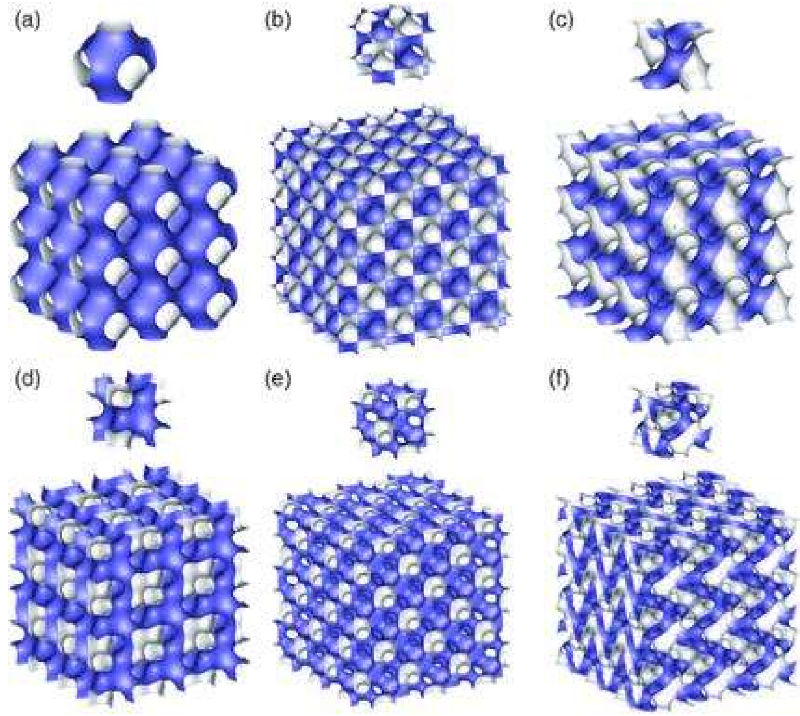

Figure 2.28: Examples of different TPMS unit cells and their corresponding lattice structures (3x3x3 tessellations) where a) Schwarz Primitive, b) Schwarz Diamond, c) Schoen Gyroid, d) Schoen I-WP, e) Schoen F-Rhombic Dodecahedra (F-RD), and f) Fischer-Koch S

(Al-Ketan and Abu Al-Rub 2019).

Because of the absence of stress-concentrators in this design, it is potentially stronger than traditional lattice designs. The other significant feature is their high surface-to-volume ratio, that makes it suitable to be used in biomedical scaffolds for tissue ingrowth (Yoo 2014). These are particularly known for metallic structures and have been used extensively in last 5 years, because of the advancements in the field of AM which has permitted the manufacturing of these intricate geometries having macropores of size ranging from 100 µm to 500 µm.

2.6.2 Family of TPMS

Schwarz reported the discovery and investigation of the first TPMS (1890). Considering a quadrilateral frame immersed in a soap-film, he obtained a structure with surfaces whose edges were four of a typical tetrahedron's six edges, and realised when they joined edge to edge, the edges transform into an infinite object's two-fold axes of symmetry (Figure 2.29). This is known as the D (Diamond) surface since the labyrinth graph show 4 'diamond' interconnected networks. Schwarz derived an analytical expression for D (Diamond) and P (Primitive) surface, for which the labyrinth graph are structures composed cube of primitive strut node and edge points. Only after this, Neovius invented the Neovius surfaces known as C (P), that are complementary to P surfaces, because P as well as C(P) represent equivalent symmetrical groups.

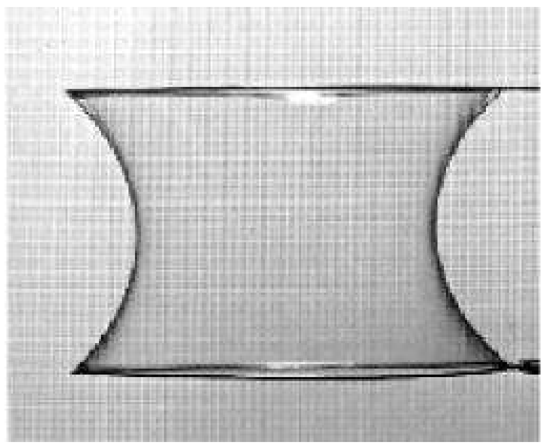

Figure 2.29: Soap film used to produce minimal surface.
(http://epinet.anu.edu.au/mathematics/minimal_surfaces)

Further advancement of TPMS occurred in 1970, when A. H. Schoen in his studies dedicated to NASA inspected if these surfaces may be used as space constructions and discovered over 12 additional examples. Surfaces having cubical symmetry were referred to as Schoen's Gyroid (G) surface. In addition, H. Karcher proved their presence in 1989 by giving mathematical confirmation and developing alternative structures with comparable surfaces.

As shown in Figure 1.28, Schwarz P (Primitive) and D (Diamond), Schoen's G (Gyroid) and IWP (I-Graph Wrapped Packages), Neovius surface, S (Fischer–Koch S), FRD, etc., are a family of TPMS that are commonly used to develop lightweight models for a variety of applications (Ahmadi et al. 2015, Rajagopalan and Robb 2006).

2.6.3 TPMS as porous scaffolds for implant applications

TPMS based scaffolds have emerged to be an ideal candidate for the reconstruction of segmental defects because of their biomorphic and bio-mimicking properties (Al-Ketan and Abu Al-Rub 2019, Yánez et al. 2018). TPMS-based scaffolds have piqued the interest of researchers not only in biomedical engineering but also in thermal, mechanical, and aeronautical engineering, due to advancements in three-dimensional modelling and printing techniques (Feng et al. 2022). To improve the integrity of the bone-implant interface, these TPMS-based porous scaffolds offer the essential support and assist in cell adhesion, proliferation, and differentiation. This increases biomechanical compatibility and durability while significantly reducing the risk of bone resorption caused by the stress shielding effect. Compared to solid implants with flat surfaces possessing a poorer tissue regeneration profile, uniformly derived TPMS lattice scaffolds provide better bone ingrowth. Besides this, they stimulate excellent cellular processes of gaseous diffusion, ionic interactions, and fluid transportation (Bobbert et al. 2017). Both numerical and experimental analysis of the TPMS scaffolds is presented extensively in the literature that illustrates its multifunctional behaviour (Abueidda et al. 2019, Herrera et al. 2014, Wieding et al. 2014, Maskery et al. 2018).

The morphological characteristics and complexity of human bone are efficiently mimicked by TPMS-based bone scaffolds. TPMS-based porous scaffold model is optimized and fabricated by additive manufacturing (3D printing) to experimentally obtain the mechanical properties within the range to reduce the bone resorption as much as possible (Wang et al. 2016). Moreover, orthopaedic surgeons still continue to face difficulties in repairing significant bone abnormalities. Therefore, the main objective to produce a subject-specific SBD scaffold with intricate patterns and structures may be accomplished by using the simplest possible design and advanced manufacturing techniques. In terms of design- freedom, and flexibility, additive manufacturing (3D printing) technology differs from traditional (Conventional rapid prototyping) approaches that are equally cost and time-consuming (Cronskäre et al. 2013). This is effectively used in orthopaedic implant modelling and fabrication of geometrically complex bio-scaffolds, preclinical treatment of challenging situations, as well as in fabrication of patient-specific devices and scaffolds to mimic the anatomical structure so as to achieve reconstruction failure (Wong et al. 2012, Ariz et al. 2021).

In orthopaedic applications, the advancements in applications of porous metal implants have reported favourable outcomes. Triply periodic minimum surface (TPMS) based structures represent exceptional performance compared to other porous structures. Bobbert et al. recently showed that a TPMS structure has tremendous capability to significantly reduce the stiffness thereby maintaining a higher strength. They have also proved to be exceptionally good in terms of permeability to provide nutrition support and bone ingrowth resembling the cancellous bones (Bobbert et al. 2017). In the similar fashion, Al-Ketan et al. studied the mechanical characteristics of TPMS and strut-based structures. As per their findings, the TPMS structure demonstrated exceptional mechanical qualities in all evaluated models (Al-Ketan et al. 2018).

2.7 Fabrication of porous scaffolds for orthopaedic applications

With the advancements in the field of manufacturing technology, specifically bio-fabrication (additive bio-manufacturing) technique has evolved as a solution to many existing issues in the area of tissue engineering (Madrid et al. 2019, Yuan et al. 2019, Bai et al. 2019). It has the potential to develop complex customised porous geometries of any desired shape and porosity. Manufacturing approaches for three dimensional porous implants are broadly classified as: conventional techniques and additive manufacturing (3D printing) technology. (Bártolo et al. 2012, Hutmacher et al. 2008).

2.7.1 Conventional Manufacturing Methods

A wide range of traditional approaches are involved in the fabrication process of porous metal implants which include solvent casting and particulate leaching (SCPL), phase separation, foaming, gas saturation, electrospinning, etc. (Reignier and Huneault 2006, Gomes and Reis 2004, Ma 2004, Yang et al. 2001).

These approaches have significant drawbacks, including the inability to appropriately manage pore size, shape, and spatial distribution of pores, as well as the inability to build internal channels inside the scaffold (Yeong et al. 2004). Modifications in processing parameter may change the morphology of pores, but the final arrangement of pores in the developed scaffold is randomized. As a result of this, pore segments not fully interlinked or having deformed paths, obstruct the nutrition transport and tissue ingrowth inside the scaffold. All such methods require intense workforce taking prolonged manufacturing hours and also usually involve harmful chemicals, that have become serious complications. Hence the development of scaffolds that encourage bone ingrowth are difficult or may be impossible with these conventional methods, as the tissue ingrowth occurs only at the periphery of these structures. Consequently, advanced bio-manufacturing techniques can be a possible solution for fabricating porous scaffolds that have enhanced topology optimization options for the customization of porosity and integration within the scaffolds.

2.7.2 Additive Bio-manufacturing Technology

This refers to the process of additive manufacturing in medical applications.

Additive bio-manufacturing or bio-fabrication has utilized the advancements of imaging technology to produce patient specific medical devices (Bártolo et al. 2009b). Presently, available commercial software may help in developing a 3D model from CT data, and bio-fabrication techniques enable the design freedom like optimal geometry or complicated bone morphology. The surgical instruments also have material flexibility; tailored for the specific use, with metallic or plastic components (Wong et al. 2012). In medical applications, additive bio-manufacturing has a restriction that it is essential to apply post-treatment of produced parts. However, due to the daily changing requirements of medical field, these techniques need to advance rapidly. The flowchart and design criteria shown in Figure 2.30 explains the necessary steps involved in the process of bio-manufacturing to develop a metal implant or scaffold.

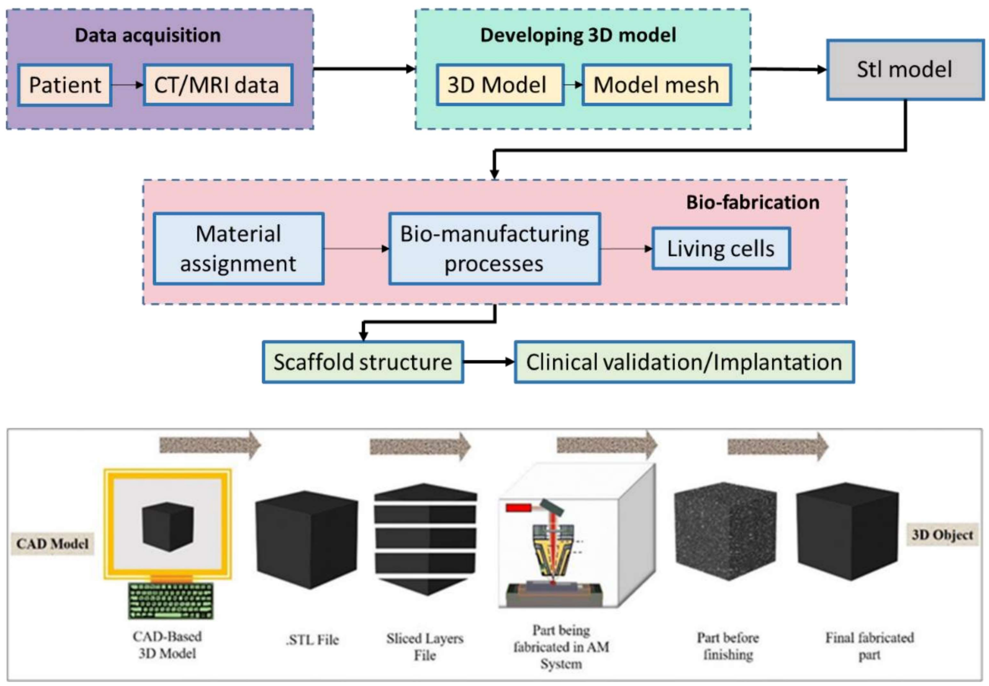

Figure 2.30: Bio-manufacturing process illustrated with a flowchart and detailed design strategy (Guddati et al. 2019).

Various fabrication methods that are used in additive bio-manufacturing technology, are shown in Figure 2.31 (Bártolo et al. 2008).

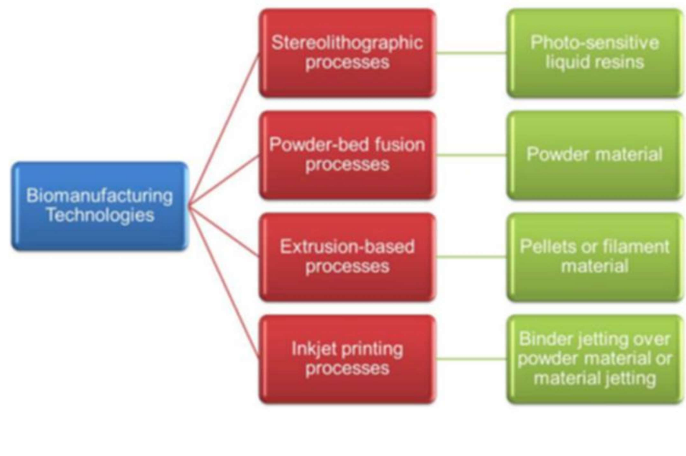

Figure 2.31: Classification of additive technologies for developing porous structures.

Presently, the most widely used additive bio-manufacturing process with metallic implants include powder bed fusion (PBF) method. The printing is performed in layers and requires powders for printing as shown in figure 2.32 (a). It has the potential to develop every type of biomaterial provided it can generate powders, where the topology of powdered particles influences the processing efficiency. With the optimization of processing factors, it is possible to enhance the surface and mechanical characteristics, thereby ensuring improved efficiency of implant.

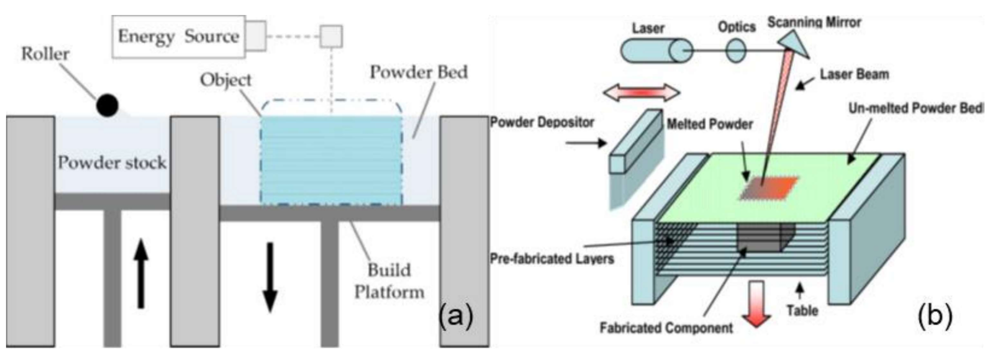

Figure 2.32: (a) Schematic of Powder Bed Fusion process and (b) demonstration of the SLM technology

For developing an implant, PBF technique includes several methods like SLS (Selective Laser Sintering), SLM (Selective Laser Melting), and EBM (Electron Beam Melting). Simplest of all being the SLS, is devoid of support structures but can be used for a wide variety of materials mainly for polymers and metal powder processing. SLM is preferred over SLS for two reasons. First, in terms of surface finish and second being its applicability to a variety of metallic materials like titanium (Ti) and its alloys, cobalt chromium (CoCr) alloys, stainless steel, etc. [22–24]. This method incorporates a layer-by-layer building pattern of a structure obtained from CAD model (Figure 2.32 (b)). The laser power significantly influences the quality of struts in SLM technology. EBM being the other method uses similar mechanism as SLM, however differing in the utilisation of energy sources. All of the aforementioned methods are based on PBF, that have the potential for accuracy requirements and mechanical capabilities for producing complicated structures. However, it is tedious and costly. Although there are various other techniques like laser engineered net shaping (LENS), electron-beam fusion (EBF), etc., but PBF is considered as a better option in regards to fabricate complex structures.

2.8 Biocompatibility of Ti and its alloys for fabrication of TPMS based scaffolds

Biocompatibility can be defined as the capability of a biomaterial to effectively respond in a therapeutic environment without causing any potential dangers to the patient, further allowing favourable tissue responses in the provided conditions to enhance the overall clinical performance of treatment procedure (Williams 2008). The biocompatibility of a particular biomaterial depends on several factors some of which include protein absorption, degradation of material and its harmful effects as well as use of patient specific/custom made implants. A scaffold's biocompatibility is mainly influenced by its material composition as well as the manufacturing procedure. Some of the main requirements for metal materials are listed in Table 2.2.

Table 2.2: Major requirements for load-bearing metallic biomaterials (Williams 2008).

Biomechanical requirements	Biological requirements
Stiffness	Biocompatibility
Strength	Surface state
Fracture toughness	Osseointegration
Wear resistance	
Fatigue strength	
Corrosion resistance	

2.8.1 Titanium versus other alloys:

The most frequently employed metals in orthopaedics are Titanium and its alloy including cp-Ti and Ti6Al4V (Liu et al. 2004, Bertol et al. 2010), NiTi (Rahmanian et al. 2014), Ti6Al7Nb (Pawlak et al. 2015) etc., cobalt-chromium including CoCr and CoCrMo alloys (Stenlund et al. 2015), and stainless steel including 316L SS (Wehmöller et al. 2005). Figure 2.33 shows some frequently used biomaterials as implants.

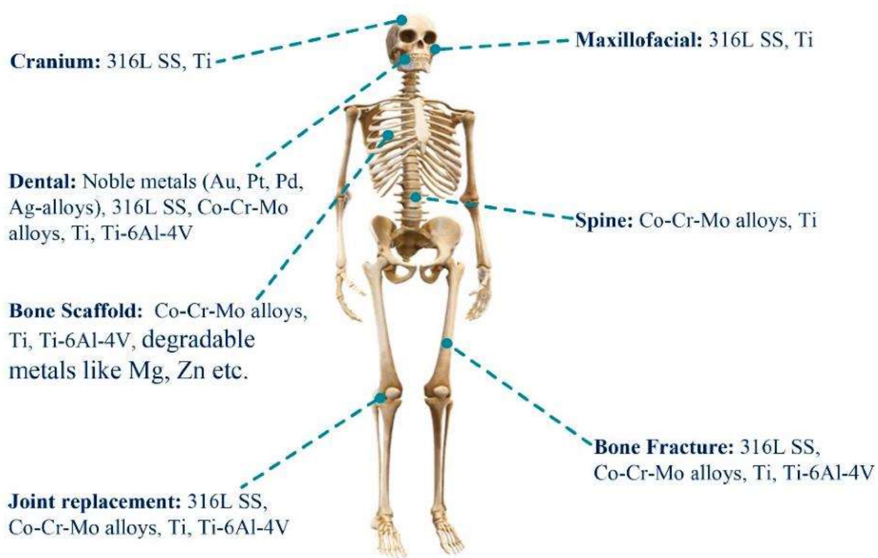

Figure 2.33: The clinical application of common metal implants (Bai et al. 2019).

ISO 13314: 2011 defined some necessary parameters that serve as the foundation for implant material selection. These include material characteristics, morphology, and mechanical as well as biological behaviour. Table 2.3 provides a comparative analysis of the mechanical characteristics of frequently utilised biomaterials.

Table 2.3: Mechanical properties of most common biomedical metal alloys (Li et al. 2014).

Metal	ρ (g/cc)	E (GPa)	Y.S (MPa)	Y.S / ρ	Fatigue strength (MPa)	% El
316L SS	7.9	210	450	57	250	40
CoCr (as cast)	8.3	200	500	60	300	8
CoNiCrMo (as wrought)	9.2	220	850	92	500	20
Ti6Al4V	4.5	105	900	200	500	13
Cp – Ti	4.5	100	300	67	200	40

2.8.2 Advantages of Ti6Al4V:

TI6Al4V are highly preferred titanium alloy among the commercially available medical grade alloys as they provide desired qualities like biocompatible behaviour, resistance to corrosion, stability, durability, and most importantly the low modulus of elasticity (Long and Rack 1998). Composition of Ti6Al4V is mention in Table 2.4.

Table 2.4: Composition of Ti6Al4V (Grade 5) alloy in % wt (Breme et al. 2016).

Chemical composition	Ti	Al	V	Sn	Zr	Mo	C	Si	Cr	Ni	Fe	Cu	Nb
Weight (%)	90	5.48	4.22	0.06	0.002	0.10	0.36	0.02	0.009	<0.001	0.11	<0.02	0.03

It has a low elastic modulus than Co-Cr alloys and stainless steel (Hanawa 2019), hence are preferred for bone replacement purposes. Furthermore, due to the presence of a permanent oxide layer on the surface of these alloys, they are less prone to corrosion (Mark and Rack 1998). Although, completely solid titanium implants cause stress shielding (as discussed earlier) resulting in a decreased bone density that eventually lead to bone resorption. Therefore, to resolve this issue, medical grade Ti (T6Al4V) based porous structures with considerably low modulus of elasticity are a viable option. The material properties of Ti6Al4V are listed in Table 2.5. The porous configuration ensures a stable and durable implant providing adequate bone ingrowth.

Table 2.5: Material Properties of Ti6Al4V (Yánez et al. 2018)

Properties	Ti6Al4V
Density	4.405E-06 kg/mm^3
Elastic Modulus	107000 MPa
Poisson's Ratio	0.323
Yield strength	1098 MPa
Tangent Modulus	1332 MPa

Although, pure titanium has superior biocompatibility and is employed in stents and wires, however has insufficient mechanical strength suitable for hard tissue or load bearing applications. As a result, despite the risk of Vanadium toxicity, Ti6Al4V is recommended for load bearing implants. Eventually, the development of a permanent TiO_2 oxide layer contributes to its improved biocompatibility (Mark and Rack 1998).

Literature indicates the extensive use of medical grade titanium alloy (Ti6Al4V) for producing scaffolds with excellent mechanical and biological properties. Yan et al. investigated the mechanical characteristics of fabricated gyroid TPMS scaffolds and reported that Ti-6Al-4V TPMS scaffolds may be designed to mimic human bone while avoiding stress shielding on implant, hence improving implant longevity (Yan et al. 2015). By developing Ti-6Al-4V gyroid scaffolds with increased porosities and variable unit cell size for bone-implant application, Ataee et al. demonstrated that the ratio of elastic modulus asymmetry in orthogonal direction was equivalent to that of trabecular bone and would be advantageous for orthopedic application (Ataee et al. 2018). Ti-6Al-4V scaffolds with diamond-based pores varying from 500 to 1500 m were developed by Hrabe et al (Hrabe et al. 2011). Li et al. investigated the influence of cell morphology on the mechanical characteristics of Ti-6Al-4V scaffolds additively produced with porosities ranging from 58 to 88 % and variable unit cells (Li et al. 2014). For the treatment of segmental bone defects, Maria et al. constructed gradient Ti-6Al-4V scaffolds of bcc and diamond architectures and average gradient porosities ranging 65-21 % (Surmeneva et al. 2017). Tan et al. also provided an outstanding assessment of the mechanical characteristics and biocompatibility of porous Ti-6Al-4V scaffolds, stressing existing production difficulties, structural inadequacies, and the uncertainties of biocompatible testing (Tan et al. 2017).

2.9 Predicting the mechanical behaviour and fluid flow properties of porous materials with Finite Element Method (FEA)

This section outlines the computational approaches for predicting biomechanical and fluid flow parameters of porous materials. Mechanical analysis is an important stage for developing metallic biomaterials to determine the performance and estimate the material's behaviour.

Experimental and computational methods have been investigated and utilised to determine mechanical performance. While experimental investigations are the most realistic testing approach, computational models may produce extremely accurate estimations and are therefore a viable cost-effective option available. Furthermore, experimental investigations give little information about mechanical sensitivity at the microstructural level (Alsayednoor 2013), that could be utilised to modify the structural design internally (Smith et al. 2013).

From the 1960s, the finite element method (FEM) has been extensively utilized to address engineering issues like design and analysis, fluid dynamics, and heat exchange. Applications involving porous materials and composites too have made substantial utilisation finite element analysis approaches (Anwar et al. 2016, S. Roy et al. 2016, Shen and Brinson 2007). The solver provides the optimal solution to every integration point for each and every element after the mesh breaks down the original model into smaller, more manageable sub-models known as elements. Because of the precise approximation of the solutions compared to experimental data, the finite element method is frequently used to predict the mechanical performance of porous materials (Ghezal et al. 2013, Campoli et al. 2013). Unfortunately, computation complexity and mesh generation are significant considerations when using this technology to solve problems. Despite tremendous advancements in computational techniques over the last few decades, designing porous structures is still time consuming due to multiple micro or macro features that result in a large number of mesh components. As a result, approximations are highly imperative, such as the scaling transitions, using 2D models and unit-cell models, and even the topological modifications, etc. This section shows how these simplifications affect the mechanical and fluid flow responses of porous materials and lattices.

2.9.1 Structural analysis to study the mechanical behaviour

The porous scaffold must exhibit good mechanical properties, to sustain the load after being implanted into the human body. Static structural analysis is therefore performed to study the mechanical characteristics like Von Mises stress distribution, elastic modulus, yield strength, deformation pattern, etc. (Ali and Sen 2017). The quasi-static behaviour predicts the biomechanical properties for pre-clinical analysis to evaluate the accuracy of the developed scaffold structure using finite element method (FEM). The elastic modulus of the model is calculated from the slope of the stress-strain curve during the elastic deformation phase, as well as the compressive strength is the stress corresponding to the maximum of the stress-strain curve. The ultimate compressive stress is what defines the compressive strength. Also, this numerical simulation method helps to establish a structural-mechanical relationship by determining the effect of topological modifications (porosity, pore shape, pore size, wall/strut thickness, unit cell size, pore distribution, etc.) on the mechanical behaviour (stress-strain pattern, compressive strength, young's modulus, deformation and fatigue pattern) of a porous structure. Four distinct kinds of TPMS constructed of Ti6Al4V were examined by Bobbert et al. for their quasi-static mechanical characteristics, fatigue resistance, as well as permeability (Bobbert et al. 2017). Speirs et al. constructed three distinct unit cells involving octahedral, cellular gyroid, and sheet gyroid cells made of nitinol scaffold fabricated with SLM, to compare the mechanical properties of octahedral and gyroid unit cells. Considering equivalent volume fractions, the gyroid structure shows superior static mechanical characteristics over the octahedral structure (Speirs et al. 2017). When evaluating the structures utilised in orthopaedic implants, mechanical characteristics are crucial assessment indicators (Zhang et al. 2018, Wang et al. 2016, Cai et al. 2019). Only when specific parameters are met by the implant's mechanical qualities will it establish a good biological relationship with the host bone and address the problem of stress shielding. Furthermore, the ultimate strength of the implant's porous structure should be greater than that of the comparable segment of human bone. In order to describe the mechanical characteristics of porous materials, elastic modulus and compressive strength are two essential components. The elastic modulus matching indicates whether or not the structure can limit the effects of stress shielding issues, and the compressive strength defines the maximum load-bearing capacity of that the structure.

2.9.2 Permeability analysis to study the fluid flow response

An essential indicator of a biomimetic bone implant scaffold is nutrient exchange ability. Continuous nutrition absorption through porous channels is necessary for tissue regrowth. As a result, the structure's permeability and pressure drop must be predicted and evaluated (Peng et al. 2019, Li et al. 2020, Chao et al. 2021, Ali and Sen 2018). The permeability of scaffolds is a significant element since it influences the capability of scaffolds to transport nutrients, and cells regeneration; consequently, the permeability of the porous structure must be explored. The fluid flow parameters of a porous scaffold construction are examined using computational fluid dynamics (CFD) modelling, which calculates the pressure drop, pressure gradient, porosity, outlet flow rate, wall shear stress, and permeability. According to Impens et al., permeability affects the effectiveness of cell seeding (Impens et al. 2010). The porosity is correlated to the permeability and surface area of the porous structure, which can directly impact the efficacy of cell adhesion to the wall surfaces of the scaffold (Dias et al 2012, Torres-Sanchezet al. 2021). Higher permeability and surface area mean that the cell encounters less resistance when penetrating the scaffold. As a result, the period that the cells are attached to the scaffold surface is reduced. Increased scaffold porosity is advantageous for maintaining activity and cell growth because it can improve nutrition transportation, fulfill the oxygen deficit, and minimise clogging. However, the findings of an investigation by Ali et al. using finite element analysis to compare the gyroid and lattice-based rectangular unit cells' mechanical qualities, permeability, and wall shear stress reveal that the lattice-based rectangular construction had superior mechanical and permeability features (Ali et al. 2020).