

Chapter 2

Cancellous Bone

The metabolism of the cancellous bone is more active than cortical bone due to the dependence of bone turnover on the surface area. This led to bone loss, as usually found in the vertebrae of patients with post-menopausal osteoporosis. Bone remodeling process as described by Frost [20] more than a half of century ago had helped many specialists and researchers to better understand the progress of osteoporosis (see Chap. 1).

Cancellous bone architecture is highly heterogeneous [11, 28–30], anisotropic and skeletally site-dependent due to the difference in external mechanical stimuli [6–9]. Therefore, the mechanical properties of cancellous bone vary according to the level of physical activities [31] of individuals as well as of the bone itself [6–8]. Due to the complexity of cancellous bone structure, modes of failures are very difficult to predict and the correlation in between the morphology and failure mode is staggeringly complicated.

The permeability of cancellous bone guarantees efficient transport of nutrients through the porous structure. Furthermore, permeability is also important in the studies of bone fusion, cementing techniques, and tissue engineering scaffold. Several factors that influence permeability of the cancellous structures are porosity, architecture, mechanical properties, and viscosity [80, 82–84]. Nauman et al. [80] describes that the intertrabecular permeability depends primarily on the flow direction relative to the principal trabecular orientation as well as anatomic site, and was less dependent on volume fraction.

2.1 Physiology

Bone is a complex organ which plays a major role in movement, protection, support, mineral storage, and formation of blood cells in a human body [32]. Bone tissue can be divided into two types of different apparent density; cortical or compact bone (high density), and trabecular or porous bone (low density) as shown

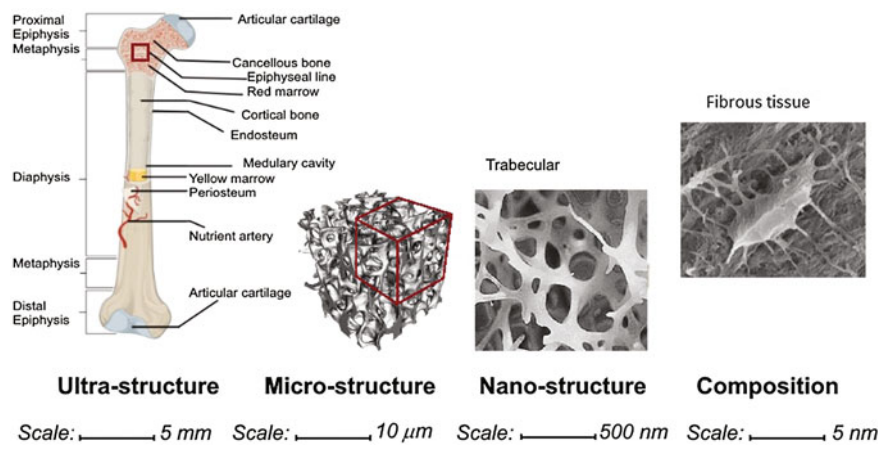


Fig. 2.1 Bone structure at different length scale in hierarchical order

in Fig. 2.1. Both cortical and trabecular bone have different loading adaptation upon physiological activities and across skeletal sites, thus contributing in different mechanical properties. Compact bone tissue is developed by Harversian systems in which is known to resist the mechanical shock. In human body, cortical bone makes up for about 80% of total bone mass. On the other hand, trabecular tissue imparts strength which holds marrow, a substance involved in producing blood cells. Stresses in bone signal the osteoblasts to deposit minerals more than osteoclasts withdrawals resulting in denser and stronger bone. However, mineral withdrawals prevail in injured bones. Furthermore, as people aged, physical activities are less, the formation of bone cells declines, calcium is lost, protein is over-consumed, and sex hormone is deficient. All these are the contributing factors of osteoporosis [32].

According to Wolff’s law, bone has its turnover in term of modeling or remodeling in which the healing process of damaged tissue deforms its structure particularly on the trabecular bone upon the applied stress [3]. The process of bone remodeling starts with the activation of osteoclasts (bone cell) followed by resorption phase. Then, osteoblast precursors are recruited, proliferated, and differentiated into mature osteoblasts. New bone matrix is then secreted and mineralized for new bone formation. Both resorption and formation of bone is load dependent, especially in the trabeculae envelope due to the large surface area (Fig. 2.2). These conditions serve a surplus of trabecular structure to maintain cell growth over the whole structure as the surface and marrow are touched. Bone starts to remodel in between endocortical, trabecular bone, and intra-cortical component of endosteal envelope [4]. This process responds to injuries such as fractures, microdamage from daily routine, and functional demands of mechanical loading. Through remodeling, bone has competency to self-heal from microdamage and macro-cracking with combined actions of both mechanical loading and biological changes.

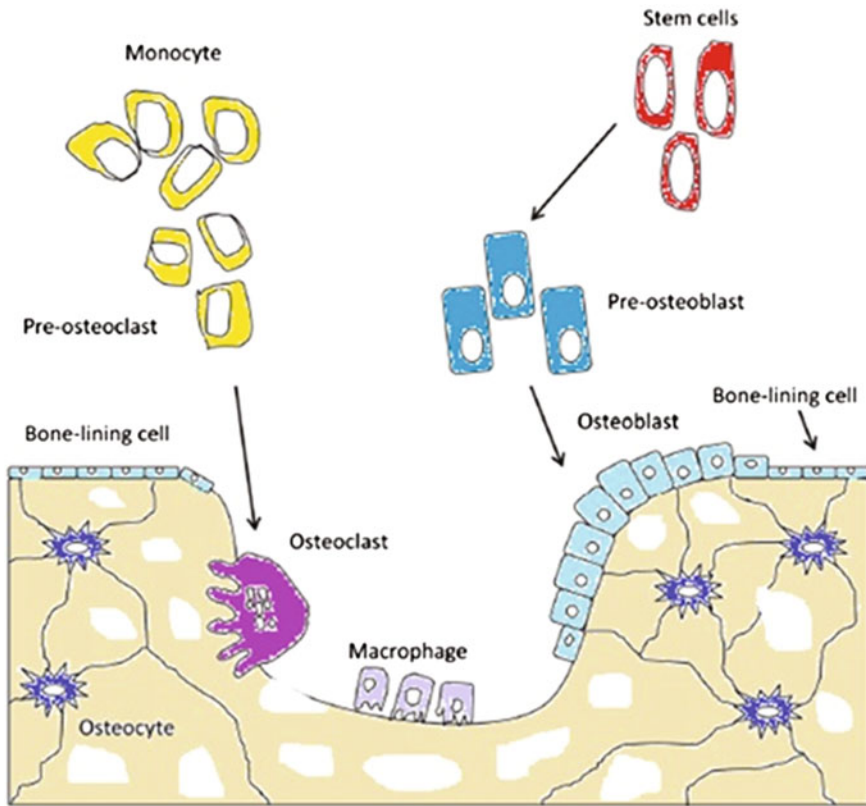


Fig. 2.2 Bone remodeling cycle. Adapted from [33]

2.2 Material Properties

Trabecular bone has a spongy-like structure with complex microarchitecture as shown in Fig. 2.3. It is found beneath cortical bone which consists of a meshwork of bony bar or plate and rod, or combination of both with many interconnecting spaces containing marrow. Trabecular bone is normally found in epiphyseal and metaphyseal region of long bone as well as in the central part of vertebrae and flat bone. The composition and distribution of trabecular bone varies across the anatomic sites and species. Unlike cortical bone, trabecular bone has a more porous, less stiffness, and softer, but higher in surface area which makes it ideal for bone remodeling process. Interaction of the marrow and the trabecular structure to adapt mechanical load during physiological event efficiently transports nutrients, giving the bone significant effect on its strength and stiffness. Additionally, the complex microarchitecture of trabecular served unique mechanical properties with complex reaction upon external loading. The trabecular microarchitecture and porosity

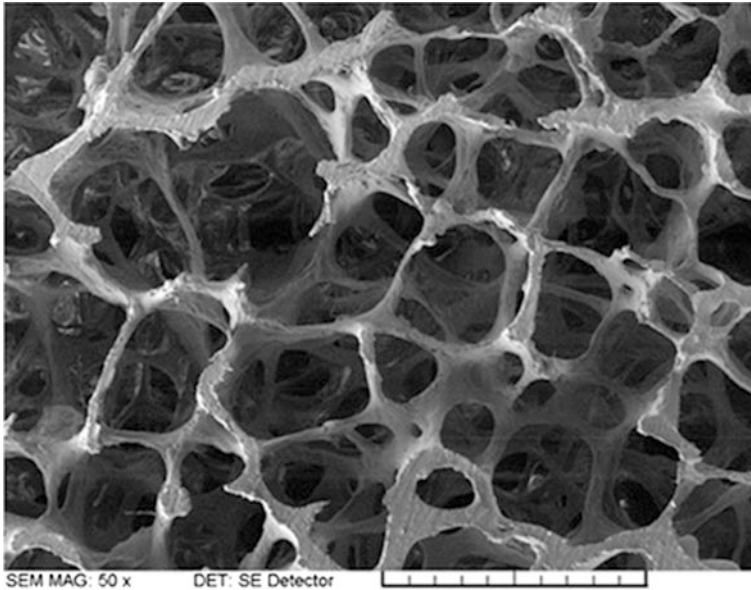


Fig. 2.3 Typical scanning electron micrograph image of cancellous bone structure showing complex arrangement of trabecular struts

depend on several factors which include anatomical sites, species, age, as well as physiological loading [34, 35]. The study on trabecular bone is important as it is associated with age-related diseases such as osteoporosis, and stress fracture in youngsters. The scope of the current work only involved trabecular bone as the subject material, thus review and discussion are limited on studies of the trabecular bone.

Trabecular bone has a very complex microarchitecture which is highly heterogeneous and anisotropic. Figure 2.4 shows in situ two porous structures of trabecular bone with and without bone marrow in normal condition. The trabecular bone architecture is distributed uniquely across anatomic sites as an adaption on a very specific physiological load. In the vertebrae for instance, the density and architecture has been observed to be varied along the superior–inferior as well as posterior–anterior directions [36, 37]. The morphological indices are contingent on BMD and changes in BMD might be due to various loading adaptation and mechanical response to biological environment to maintain their structural integrity. The microarchitecture of trabecular bone gives the bone a unique mechanical property relative to its strength and elasticity. Mechanical properties of trabecular bone are presented typically by stress–strain relationships, in which a clear linear region is absent and the yield point is uncertain.

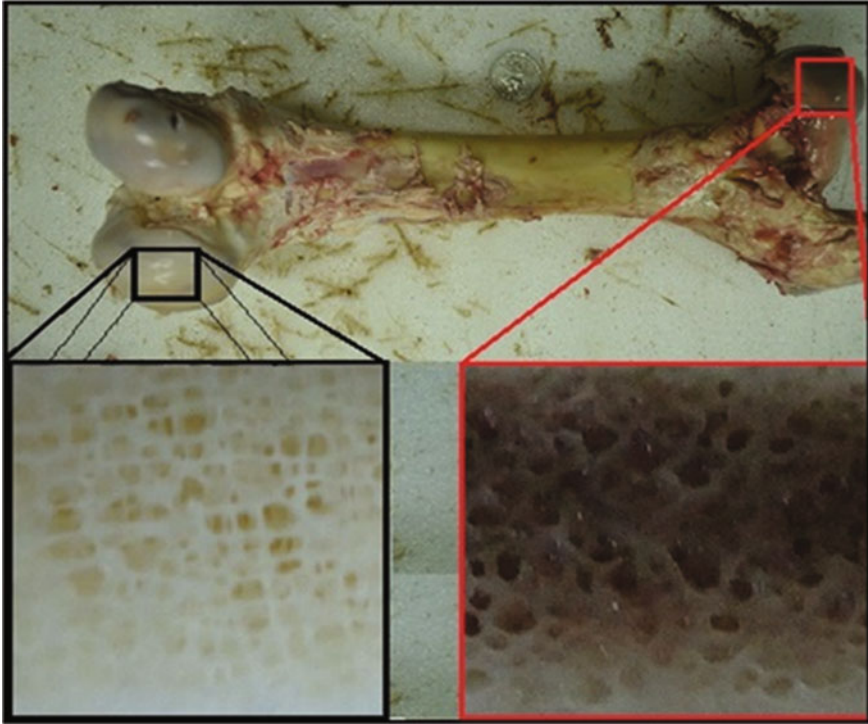


Fig. 2.4 Femoral bone with entrapped marrow (shown in *red box*) and without marrow (shown in *black box*) at different cancellous bone region

2.3 Bone Disease

An imbalance in bone remodeling process usually leads to bone loss. This happens as the formation of the bone is at slower rate than the breakdown of the bone. Most diseases due to bone loss are discussed here in this section. The bone mass begins to deteriorate after about 30.5 years of life. It is reported that only 70% of young adult bone mass at most will be remained at the age of 70 [38]. However, the loss of bone are scattered across the skeletal sites and women suffer earlier bone loss at double rate compared to men. Bone architecture and collagen cross-linkage and size are also factors contributing to the loss of bone mass and strength. Other than that, the calcium apatite crystals conformity and disruption of bone cell signaling for osteoclasts and osteoblasts are also limited at older ages.

2.4 Osteoporosis

The most common bone disease is osteoporosis, in which bone mass is found low and bone structure is deteriorated resulting in fragile bone and fracture risk (Fig. 2.5). Bone fractures occur mostly in individuals with osteoporosis causing strength and vitality impairment of the body. Further, it can negatively affect the patient psychologically. Commonly, the disease affects most of the skeleton and is known as generalized osteoporosis. However, the disease can also be local, affecting specific site of the skeleton. This is usually caused by injury or reduction in muscular force onto the bone as found in limb paralysis.

Osteoporosis is mostly related to aging which caused bone losses and deteriorate its structure. This phenomenon is known as 'primary osteoporosis', which can be prevented to minimize its effects with improved diets and physical activities. There are also several treatments available. The spinal deformity in osteoporosis progresses as shown in Fig. 2.6. Height can be seen to reduce as the thoracic vertebrae fractured by compression and as the thoracic kyphosis progresses. Further,

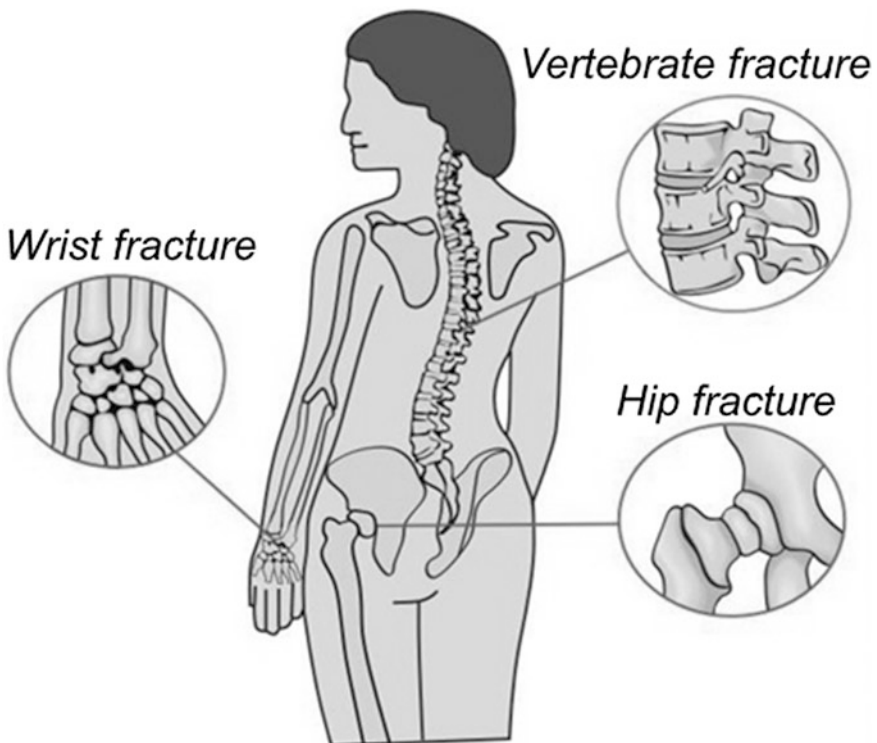


Fig. 2.5 Osteoporotic fracture-prone areas of the skeleton

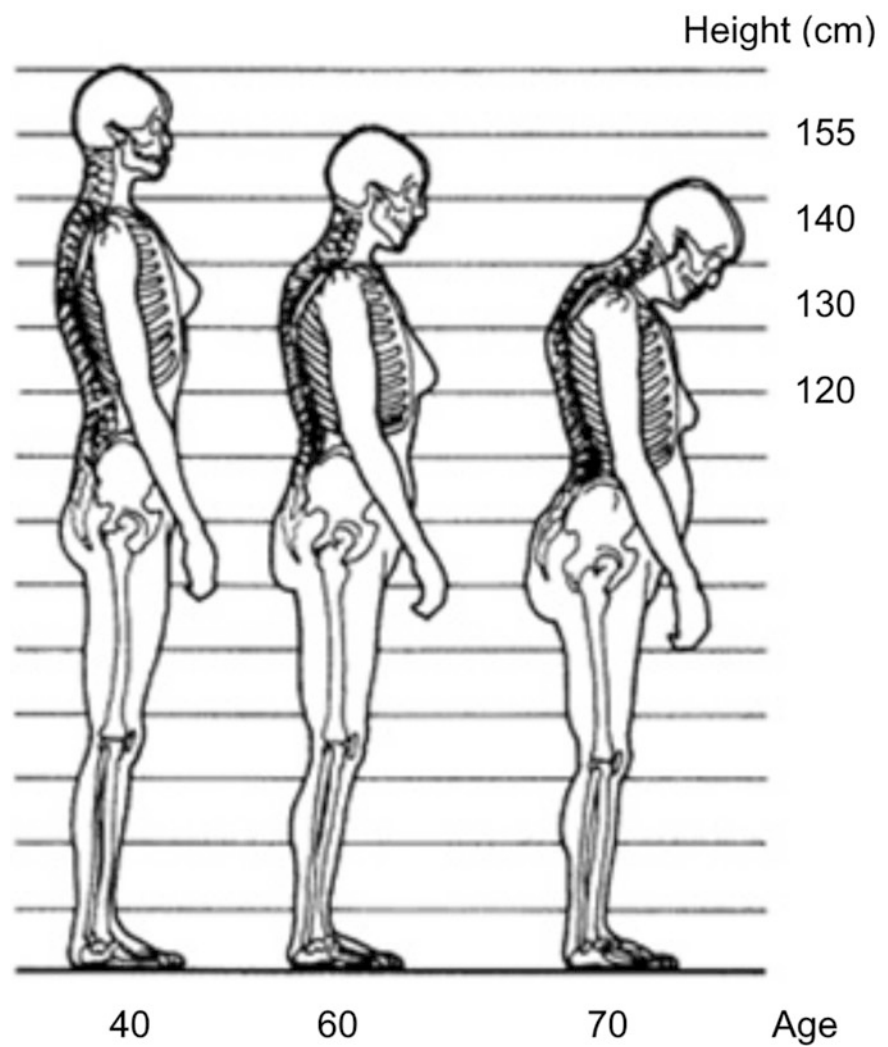


Fig. 2.6 Osteoporotic progression

abdominal distention occurs as a result of pressure on viscera when the lower ribs subsequently rest on ileac crest.

However, osteoporosis may also be initiated by other diseases, and some medications and toxic agents as shown in Table 2.1. This type of osteoporosis is known as ‘secondary osteoporosis’, which can be prevented—if recognized early—through nutritional plan and physical activity, along with therapy when necessary.

Table 2.1 List of diseases which contributed to secondary osteoporosis [39]

Genetic disorders	Hypogonadal states	Endocrine disorders	Gastrointestinal diseases	Hematologic disorders	Rheumatic and auto-immune diseases	Miscellaneous
Cystic fibrosis Ehlers-danlos Glycogen storage diseases Gaucher's disease Hemochromatosis Homocystinuria Hypophosphatasia Idiopathic hypercalciuria Marfan syndrome Menkes steely hair syndrome Osteogenesis imperfecta Porphyria Riley-day syndrome	Androgen insensitivity Anorexia nervosa Athletic amenorrhea Hyperprolactinemia Panhypopituitarism Premature ovarian failure Turner's and Klinefelter's syndrome	Acromegaly Adrenal insufficiency Cushing's syndrome Diabetes mellitus (Type 1) Hyperparathyroidism Thyrotoxicosis	Gastrectomy Inflammatory Bowel disease Malabsorption Celiac disease Primary biliary cirrhosis	Hemophilia Leukemia and lymphomas Multiple myeloma Sickle cell disease Systemic mastocytosis Thalassemia	Ankylosing spondylitis Lupus Rheumatoid arthritis	Alcoholism Amyloidosis Chronic metabolic acidosis Congestive heart failure Depression Emphysema End stage renal disease Epilepsy Idiopathic scoliosis Immobilization Multiple sclerosis Muscular dystrophy Post-transplant bone disease Sarcoidosis

2.5 Rickets and Osteomalacia

Rickets in children also happen as a result of other diseases. Rickets is initiated from insufficient calcium phosphate mineral which is essential for bone growth. This condition causes deformities of the bones, especially bowed legs in children or known as osteomalacia in adults. While these diseases can be prevented with adequate supply of vitamin D, but oftentimes devastated the life of the affected individuals.

Rickets and osteomalacia can also be developed as a result of chronic renal disease [40]. Furthermore, the patients may also be at risk of renal osteodystrophy, a complex bone disease which stimulate bone metabolism and may develop adynamic bone disease. The progress of this disease in patients has no effect against dialysis and transplantation.

2.6 Paget's Disease

Paget's disease is always characterized by bone losses due to overactive osteoclast. It oftentimes affect specific bone site such as the spine, pelvis, legs, or skull. This condition leads to increase bone formation, but with scrambling structure. Thus the newly formed bone is larger in size with enhance number of blood vessels and connective tissue in marrow. The bone will have high tendency to deform and fracture. Early diagnosis helps in minimizing the impact of the disease on patients' vitality.

2.7 Mechanical Properties of Cancellous Bone

Cancellous bones have been extensively studied and the research work started as early as 1866 by GH Meyer who demonstrated the structure of cancellous bone. Singh [41] described the correlation of cancellous bone orientation with stress direction, but with inadequate description of basic architecture. The measurement of bone microarchitecture has been done in both two-dimensional (2D) [42–44] and three-dimensional (3D) analyses [45, 46]. Due to inherent limitations and unexplained variation of 2D analysis, the 3D analysis has gained popularity. 3D model of the bone is reconstructed from micro-computed tomography (μ -CT) stacked images. Structural indices utilizing the 3D model have been analyzed using direct structural analysis technique [47].

From an engineering point of view, cancellous bone is an anisotropic, highly complex structure. It demonstrates different properties in compression, tension, and

shear, as well as across anatomical sites. In the development of synthetic cancellous bone structure, the microarchitecture is of primary importance as it is highly correlated to mechanical properties. Liu et al. [48] showed that cancellous bone architecture plays an important role as it takes 75% of the external loading through the cortical bone. The size and architecture of cancellous bone strongly affect the fracture resistance of the bone under load [17].

The studies of cancellous bone morphology which describes the shape, size, and structural orientation have been carried out by numerous researchers. The morphology and bone density change with age, however, the changes are specific to individual trabecular only [49]. Other researchers found the relationship between morphological parameter that describes the architecture of cancellous bone, such as in between bone volume fraction (BV/TV) and the apparent elastic properties [50, 51]. Previously, measurement of bone mineral density was used as a method to predict or diagnose bone osteoporosis. These measurements are standard for bone osteoporosis. However, this method could not predict changes in an individual strut of cancellous bone structure as it does not take into account the influence of trabeculae changes in cancellous bone quality [11, 52–54]. With a new technology in scanning tomography of cancellous bone, the reconstruction of cancellous bone has become more accurate and in details. μ -CT scan and micro-MRI technology are now possible to assess cancellous bone morphology in detailed 3D. The direct examination of 3D bone architecture in vitro by computed tomography was started by Feldkamp [55], followed by Wehrli [56] and R  gsegger [57]. The understanding of tissue level yielding in cancellous bone could be obtained through morphological analysis. The detail morphological parameter commonly evaluated are; trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp), bone volume fraction (BV/TV), structure model index (SMI), connectivity density (Conn.D), degree of anisotropy (D.A), [11, 49, 51, 58–64], Plate-like trabecular (P), and Rod-like trabecular (R) [65, 66].

The changes in the morphology of cancellous bone are caused by the remodeling process in order to achieve optimum state through metabolic activities of many cells at the osteonal and trabecular level. As mentioned before, aging and bone density also affect bone morphology. The mechanical properties of cancellous bone depend on the porosity, specific surface area, volume fraction, and architecture or physical arrangement of solid bone tissue [49, 67]. The trabeculae changes from a plate-like structure to a rod-like structure (trabecular thinning) during aging or due to an imbalance of bone remodeling [21, 68, 69].

Direct and various morphological parameters for trabecular bone have been quantified by model-independent method [6, 70]. Additionally, the morphological parameters of trabecular bone can be extracted through scanning process which was measured through stacked image files. Computational tools for analysis of trabecular geometry and whole bone shape such as BoneJ in ImageJ [71] are used to measure detail morphological parameters of trabecular bone (Table 2.2).

Table 2.2 Definition of morphological parameters for trabecular bone sample which can be obtained from BoneJ analysis in ImageJ

Degree of anisotropy (DA)	Measure of how highly oriented substructures are within a volume [66]
Connectivity density (Conn.D)	Divide the connectivity estimate by the volume of the sample [66]
Structure model index (SMI)	Determine the plate- or rod-like geometry of trabecular structures [72]
Trabecular thickness (Tb.Th) and trabecular separation (Tb.Sp)	Define thickness at a point as the diameter of the greatest sphere that fits within the structure and which contains the point [73]
Bone volume fraction (BV/TV)	The volume of mineralized bone per unit volume of the sample [71]

From Tables 2.3 and 2.4, it can be seen that trabecular bone morphology varies across anatomic sites. The trabecular bone microstructure parameters are also different between human and animal, as studied by Teo et al. [74]. They compared the trabecular bone parameters between human femoral, human lumbar, sheep femoral, and pig lumbar. They discovered that the bone volume fraction in sheep femoral was the highest among the groups. It was also found that human lumbar trabecular bone had the lowest bone volume fraction, which was only 8%. In addition, they stated that the trabecular thickness, trabecular number, and trabecular separation of pig lumbar and human femoral are very similar.

To determine this complex material architecture, various mathematical integrations were employed in computational methods; with the most standardized application presented in Bone [71]. This is due to incapacity of manual calculation of the stated morphological parameters through experimental analysis. Bone J measures morphological indices while the FE method is employed in order to acquire both 3D microarchitecture as well as to predict the mechanical properties of this kind of bone material [90]. The 3D models are built up from a series of imaging techniques which converted 2D stacked images into a complete model in 3D based on the coordinates and size [91]. Thorough the understanding of the morphological parameters and microarchitecture responses of the trabecular bone, scientists can improve the prediction of the bone's mechanical strength and failure behavior. Thus, this method can benefit the more advanced analyses of failure prediction and may improve the diagnosis and treatment of osteoporosis.

Both physiological and traumatic loadings are complex and multiaxial in nature, which involved different loading pattern in medial, lateral, longitudinal, or transverse region following bone adaptation [92]. For example, the gait analysis of the femur indicated that the femoral head bears 234% of the body weight during the stance phase of walking [93, 94]. On the other hand, the hip joint suffers 85% of the total impact force during sideways fall to the hip [95]. However, studies with proper

Table 2.3 Variation in trabecular parameters studies on human bone

Authors	Bone types	Bv/tv (%)	Thickness			Density (g/cm ³)
			Tb.Th (mm)	Tb.N (mm ⁻¹)	Tb.Sp (mm)	
Rho et al. [75]	Human femoral	0.26 (0.07)	0.12 (0.03)	2.11 (0.26)	0.36 (0.08)	–
	Human lumbar	0.08 (0.03)	0.06 (0.02)	1.30 (0.23)	0.65 (0.16)	–
Nicholson et al. [76]	Lumbar vertebral	0.08 (0.03)	0.06 (0.01)	1.27 (0.23)	0.75 (0.16)	± 0.15 (0.04)
Portero-muzy et al. [77]	Right oscalcis	11.40 (3.5)	0.12 (0.02)	0.96 (0.18)	0.97 (0.22)	± 0.31 (0.08)
Martin Hudelmaier et al. [78]		F = 40 (4) M = 43 (4)	F = 1.87 (0.15) M = 1.87 (0.19)	F = 1.87 (0.15) M = 1.87 (0.19)	F = 0.32 (0.05) M = 0.30 (0.04)	F = 0.18 (0.04) M = 0.14 (0.02)
Majumdar et al. [65]	Calcaneus	± 0.26 (0.13)	± 0.17 (0.05)	± 1.46 (0.34)	± 0.54 (0.2)	–
	Distal femur	± 0.27 (0.15)	± 0.20 (0.07)	± 1.47 (0.37)	± 0.45 (0.22)	–
	Proximal femur	± 0.27 (0.15)	± 0.19 (0.04)	± 1.29 (0.39)	± 0.65 (0.32)	–
	Vertebrae	± 0.17 (0.08)	± 0.17 (0.02)	± 0.95 (0.37)	± 1.11 (0.7)	–
Anderson and Carman [79]	Human femoral head medial group bone	0.27 (0.06)	–	1.53 (0.16)	–	–
Goulet et al. [80]	Proximal tibia, proximal and distal femora, iliac crest, distal radius, proximal humerus, and the lumbar vertebral bodies	0.20 (0.07)	0.14 (0.02)	1.39 (0.32)	0.64 (0.24)	0.31 (0.12)
Morgan [81]	Greater trochanter	–	1.14 (0.01)	1.02 (0.17)	0.96 (0.19)	–
	Proximal tibia	–	0.13 (0.01)	1.18 (0.15)	0.80 (0.09)	–
	Femoral neck	–	0.20 (0.03)	1.60 (0.19)	0.61 (0.09)	–
Kleerekoper et al. [82]	Fracture	–	0.12 (0.03)	–	0.71 (0.181)	1.26 (0.26)*
	Non-Fracture	–	0.15 (0.03)	–	0.85 (0.148)	1.03 (0.15)*

(continued)

Table 2.3 (continued)

Authors	Bone types	Bv/tv (%)	Thickness			Density (g/cm ³)
			Tb.Th (mm)	Tb.N (mm ⁻¹)	Tb.Sp (mm)	
Hildebrand et al. [83]	Iliac crest	0.16 (0.05)	0.15 (0.03)	1.40 (0.27)	0.75 (0.150)	–
	Second lumbar spine	0.08 (0.02)	0.12 (0.02)	1.28 (0.20)	0.79 (0.135)	–
	Fourth lumbar spine	0.09 (0.03)	0.14 (0.03)	1.16 (0.18)	0.85 (0.143)	–
	Femoral head	0.26 (0.08)	0.12 (0.03)	1.60 (0.29)	0.64 (0.114)	–
	Calcaneal core	0.12 (0.04)	0.13 (0.02)	1.46 (0.20)	0.68 (0.107)	–
Yeni et al. [84]	Thoracic	0.14 (0.05)	0.23 (0.02)	0.63 (0.15)	1.47 (0.486)	–
	Lumbar	0.15 (0.04)	0.23 (0.02)	0.63 (0.15)	1.47 (0.494)	–
Nicholson and Strelizki [85]	Calcaneus	–	–	–	–	± 0.32 (0.07)

*Bone density/mm

Values in parenthesis are the corresponded ± S.D

F Female, M Male

experimental conditions or biomechanical models that account for in vivo loading complexities are lacking. Furthermore, biological variations and other associated uncertainties which include the interaction with other organs and body systems hinder precise estimation on conditions that can be implemented in vitro.

According to Cowin et al. [23], factors of bone fracture risk can be categorized as follows:

- i. age or age-related,
- ii. genetics and environmental,
- iii. endogenous hormones,
- iv. chronic diseases,
- v. physical characteristics of bone.

Interests in mechanical properties of trabecular bone are related to its importance in the early development of bone regenerative solution and bone analogous materials such as bone grafts, implants, or bone synthetic and as an alternative solution for in vitro biomechanical test substrates. Trabecular bone is considered as the most important structure for load-bearing applications as it supports more than 75% of the body weight [96, 97]. In addition, the adjacent load through cortical bone is also bore by the trabecular bone, making it a more proficient microarchitecture in

Table 2.4 Various morphological parameters on various animals

Authors	Animal	Anatomy	Number of sample	BV/TV	Thickness		
					Tb.Th (mm)	Tb.N (1/mm)	Tb.Sp (mm)
Teo et al. [74]	Pig	Lumbar	–	0.12–0.30	0.08–0.14	1.27–2.79	0.27–0.46
Linde et al. [86]	Sheep	Femoral	–	0.28 (0.07)	0.19 (0.05)	1.70 (0.13)	0.53 (0.05)
Shi et al. [49]	Bovine	Tibial	–	–	0.18 (0.03)	–	0.61 (0.08)
Morgan et al. [81]	Bovine	Tibial	7	–	0.14 (0.01)	1.66 (0.13)	0.55 (0.04)
Yao et al. [87]	Rabbit	Sagittal	6	0.43 (0.48)	0.12 (0.01)	3.56 (0.11)	0.16 (0.02)
		Coronal	7	0.46 (0.53)	0.13 (0.01)	3.52 (0.26)	0.15 (0.02)
Teng and Herring [88]	Pig	Sagittal	–	–	0.18 (0.04)	2.40 (0.40)	0.27 (0.05)
		Frontal	–	–	0.13 (0.01)	2.90 (0.30)	0.23 (0.04)
		Horizontal	–	–	0.14 (0.02)	2.80 (0.30)	0.24 (0.02)
Mulder et al. [89]	Pig mandibular condyle	Fetal	4	0.21 (0.41)	0.05 (0.00)	6.99 (0.47)	0.12 (0.01)
		New born	4	0.20 (0.16)	0.06 (0.01)	3.95 (0.22)	0.23 (0.02)

Values in parenthesis are the corresponded $\pm$ S.D

absorbing impact through bone joint [97]. The greatest extend of knowledge in material properties of trabecular bone are required in order to optimize both the strength and ability. These properties can be acquired through mechanical testing such as compression and tensile tests, as well as computational methods including macro or micro imaging techniques and computerized simulations.

Cancellous Bone

Mechanical Characterization and Finite Element
Simulation

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2018, VIII, 72 p. 31 illus., 17 illus. in color., Hardcover

ISBN: 978-981-10-5471-6