COMPUTATIONAL MODELLING OF TRABECULAR BONE STRUCTURE USING FLUID-STRUCTURE INTERACTION APPROACH

RABIATUL ADIBAH BINTI ABDUL RAHIM

UNIVERSITI TEKNOLOGI MALAYSIA

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RABIATUL ADIBAH BINTI ABDUL RAHIM

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This work is dedicated to ALLAH SWT for all His guidance

This work is dedicated also to all my family members, as a token of love and appreciation. To my husband, Fahmi Bahri, who always loves, patient and supports me through good and bad times. To my parents for their love and always encourage me to go on every adventure, especially this one.

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ABSTRACT

While doing daily physiological activities, trabecular bone will experience certain amount of deformation, which causes movement of the bone marrow. The bone marrow movement could affect the bone remodelling process. The properties of the bone will also be affected as the bone marrow acts as a hydraulic stiffening to the trabecular structure. Previous studies on trabecular bone remodelling did not consider the effects of bone marrow movement. Thus, there is a need to perform combined analyses of the bone marrow movement with trabecular structure to assess its effects on the remodelling process under a realistic condition. The aim of this study is to determine the effect of bone marrow movement onto the trabecular bone structure under mechanical loading using fluid-structure interaction (FSI) approach. Two different models of the trabecular bone, namely idealised and actual were constructed. The idealised models were used to correlate the bone marrow behaviour to the trabecular bone morphology. The actual trabecular bone models were constructed to mimic the presence of the bone marrow within the trabecular bone structure during physiological loading. The effects of different orientation of the trabecular structures were also examined. Three numerical approaches which are finite element method, computational fluid dynamics and FSI were employed to evaluate the importance of bone marrow movement effect towards the trabecular bone mechanical properties. The findings show that the bone cells are able to stimulate the bone remodelling process under the normal walking gait loading. The bone marrow behaviour such as shear stress, pressure and permeability, together with bone porosity and surface area, have a significant relationship with a p-value < 0.05. The longitudinal permeability and stiffness were respectively 83% and 56% higher, compared to the transverse orientation. The shear stress during a normal walking phase was in a range of 0.01-0.27 Pa. These are sufficient to regulate cell response. It was also found that the stiffness of the trabecular bone structure is 22% higher compared to the models without the bone marrow. This finding suggests that the presence of the bone marrow could help to reduce the deformation and stresses on the trabecular bone structure.

ABSTRAK

Semasa melakukan aktiviti fisiologi harian, tulang trabekular akan mengalami perubahan bentuk yang menyebabkan pergerakan sumsum tulang. Pergerakan ini boleh menjejaskan proses pembentukan semula sel tulang. Sifat-sifat tulang itu sendiri juga terjejas dengan peranan sumsum tulang sebagai pengekalan hidraulik pada trabekular. Kajian terdahulu menganalisis tulang trabekular tanpa mengambil kira pergerakan sumsum tulang. Oleh itu, untuk menyerupai keadaan sebenar adalah penting untuk mempertimbangkan analisis gabungan sumsum tulang dengan struktur trabekular. Tujuan kajian ini adalah untuk mengenal pasti kesan pergerakan sumsum tulang pada struktur trabekular terhadap beban mekanikal dengan menggunakan pendekatan Interaksi Struktur-Bendalir (FSI). Dua jenis model yang berbeza iaitu model unggul dan tulang trabekular sebenar dibina. Model unggul digunakan untuk mengukur hubungan ciri-ciri sumsum tulang kepada morfologi tulang trabekular. Manakala, model tulang trabekular sebenar dibina untuk mengkaji keadaan sebenar sumsum tulang dalam struktur semasa beban fisiologi. Orientasi struktur trabecular yang berbeza juga diperiksa. Tiga pendekatan berangka yang mana merupakan kaedah unsur terhingga, dinamik cecair pengkomputeran dan FSI digunakan untuk menilai kesan kepentingan pergerakan sumsum tulang ke arah sifat mekanik tulang trabekular. Penemuan menunjukkan sel tulang mampu untuk bertindak balas terhadap proses pembentukan semula tulang dengan beban gait berjalan secara normal. Perilaku pergerakan sumsum tulang seperti tekanan ricih, tekanan dan kebolehtelapan dengan keliangan dan kawasan permukaan trabekular mempunyai hubungan yang signifikan dengan nilai-p < 0.05. Kebolehtelapan dan kekakuan orientasi membujur adalah 83% dan 56% lebih tinggi berbanding orientasi melintang. Dalam kajian beban gait, nilai tegasan ricih sepanjang fasa berjalan secara normal didapati dalam julat 0.01-0.27 Pa. Ini didapati cukup untuk mencerna tindak balas sel seperti yang dinyatakan dalam kajian sebelumnya. Kekakuan tulang trabekular adalah 22% lebih tinggi berbanding model tanpa sumsum tulang. Penemuan ini mencadangkan kehadiran sumsum tulang boleh menyebabkan perubahan bentuk dan tekanan pada struktur trabecular berkurang.

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LIST OF ABBREVIATIONS

FSI	-	Fluid-Structure Interaction
MSCs	-	Mesenchymal Stromal Cells
HSCs	-	Hematopoietic Stem Cells
MIL	-	Mean Intercept Length
SMI	-	Structure Model Index
3D	-	Three-Dimensional
FEA	-	Finite Element Analysis
µCT scan	-	Micro-Computed Tomography Scan
BV/TV	-	Bone Volume Fraction
BS/TV	-	Bone Specific Surface-To-Volume
Tb.Th	-	Trabecular Thickness
Tb.Sp	-	Trabecular Separation
Tb.N	-	Trabecular Number
Conn.D	-	Connectivity Density
DA	-	Degree of Anisotropy
QCT	-	Quantitative Computed Tomography
BMD	-	Bone Mineral Density
SI	-	Singh Index
ALE	-	Arbitrary Lagrangian-Eulerian
ANFH	-	Avascular Necrosis of The Femoral Head
S.G	-	Steroid Injection Group
C.G	-	Controlled Group
ARF	-	Activation-Resorption-Formation
BMU	-	Basic Multicellular Unit
MRI	-	Magnetic Resonance Imaging

pQCT	-	Peripheral Quantitative Computed Tomography
CSM	-	Computational Solid Mechanic
CFD	-	Computational Fluid Dynamic
BMI	-	Body Mass Index

LIST OF SYMBOLS

k - intrinsic permeability of the trabecular bone
Q - volumetric flow rate
μ - viscosity
t - specimen thickness
A - cross-section area
ΔP - pressure difference
ρ - density
u - velocity
p - pressure
ε - porosity
V_0 - total volume of the structure
V - volume that the structure occupies

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Bone is an ultimate biomaterial which is light, robust, able to adapt to its functional demand and can also repair itself. Bone roles as structural support, shield vital organs from distress, maintains mineral homoeostasis (calcium and phosphorus), and serve as attachment sites for muscles. The four shapes of bone include short, long, flat and irregular shape and different shape has different purpose and position in the human body.

There are two types of bone tissue; cortical bone and trabecular bone. As shown in Figure 1.1, the cortical bone is the outside shell of the bone that forms the tube of the long bone, while the trabecular bone is the porous cellular solid that absorb load. Up to 80% of the bone mass is composed of the cortical bone since it is compact dense and solid, and the balance, which only 20% carried by trabecular bone [1]. Due to the trabecular bone is porous structure, the bone is strong but light in weight. The cortical bone is a bone tissue that has a porosity less than about 30% [2]. Thus, porosity can be used to differentiate between the cortical bone and trabecular bone [3]. Furthermore, the trabecular bone is also known as spongy bone or cancellous bone.

The trabecular bone structures arranged in order to withstand the stresses from usual standing and walking. In addition, the irregular lattice small rods and plates on the trabecular bone tissue called trabeculae and the pores of the trabecular bone filled with bone marrow.

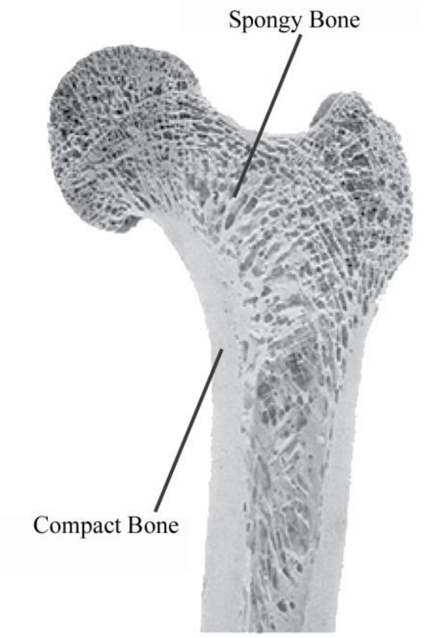

Figure 1.1: Structural types of bone; compact and spongy bone

The bone tissue is composed of organic phases, inorganic phases, and water. The organic phase consists of fibrous type I collagen and amorphous ground substance, while the inorganic phase contains calcium phosphate crystal. Organic and inorganic phase contribute to the tensile strength and compressive strength respectively to the bone tissue [4]. There are several cells in the bone such as osteoclasts, osteoblasts, osteocytes, lining cells, etc. All these bone cells have their functions in bone growth and recovery, also known as bone remodelling process.

Studies on mechanobiological movement through the trabecular bone needed to sustain the bone quality. Previous researchers reported that various physiological activities had affected the bone remodelling process and nutrient supply. Moreover, bone is well known as a self-repairing structural material that altered mechanical loading. In addition, the bone marrow contained by the trabecular bone will have displacement while bone is subject to mechanical loading.

It is widely known that the trabecular bone is a highly porous structure with a significant volume of bone marrow. A compressive or tensile force on the trabecular bone will result in bone marrow movement with respect to the trabecular bone structure. Hence, the interaction between the fluid and trabecular bone will occur, and this incident might have several effects on the trabecular structure. Therefore, the Fluid-Structure Interaction (FSI) approach were used to find out the effect of fluid to the trabecular and vice versa. With the purpose of understanding the bone marrow interaction inside the trabecular bone, the knowledge of bone marrow properties is essential. Even though there are some previous researches on bone marrow, the literature available on the fluid flow characteristic of bone marrow in the trabecular bone is still lacking. As the trabecular bone experience loading conditions, the bone marrow will have a resistance to the trabecular bone structure. Since the trabecular bone is known as an anisotropic material, by measuring the permeability of bone at a different orientation more understanding of the trabecular bone orientation can be understood. Moreover, knowledge of shear stresses that occur within the bone during daily activities is necessary to comprehend how the bone marrow can affect the trabecular structure properties.

The pressure differences across the trabecular bone along with viscosity and permeability values were used in these studies to quantify the shear stresses occurring on the trabecular surfaces. Currently, no literature is available regarding the nature and behaviour of bone marrow that occur in trabecular bone during physiological loading condition. So far, however, there has been little discussion on the fluid in bone area, and most of the researchers focused on the bone fluid flow within the lacunar-canalicular porosity. Therefore, in this study, the main concern is on the FSI of the bone marrow within the trabecular bone with the purpose of finding a correlation between fluid characteristics and mechanical properties of the trabecular bone and how the trabecular bone reacts on the interaction of bone marrow.

1.2 Problem Statement

As mentioned earlier, this study is based on the effect of bone marrow movement to the trabecular bone during the physiological activities. It is commonly known, bone marrow always coexisting with the trabecular structure. However, previously most of studies have modelled the fluids and solid components separately. Thus, unable to capture the real conditions which occur within the trabecular bone and bone marrow. Due to the load applied to the bone while daily activities were performed, such as standing, walking and running, the trabecular structure will have a stress and deformation. Consequently, the bone marrow within the trabecular would have movement, while also providing a hydraulic stiffening effect to the trabecular structure. The hydraulic stiffening effect will be slowing down the trabecular bone deformation [5]. Additionally, the movement of bone marrow can cause shear stress to the trabecular bone structure. These mechanical effects to the trabecular bone are crucial to be understood with the purpose of developing artificial trabecular bone or scaffold.

Furthermore, the mechanical environments of bone marrow are not yet clearly understood. Other than a function of hydraulic stiffening of bone, bone marrow also acts importantly in the bone remodelling process. In fact, bone marrow also functions as a home for progenitor cells; osteoclast and osteoblast, also, as a host to others cells such as immune cells, blood cells, adipocytes, mesenchymal stromal cells (MSCs), hematopoietic stem cells (HSCs), etc. [6]. The remodelling process was controlled by osteocytes mechanobiological signalling which was diffuse to the bone marrow. Likewise, it is known that when there is mechanical loading due to the physiological activities, the bone marrow within the trabecular structure was compressed. This phenomenon causes a pressure drop in the trabecular bone structure. Thus, the bone marrow will have a fluid flow through the porous structure. Furthermore, the interaction between the bone marrow flow and the trabecular wall will generate shear stress. These mechanical stimuli will affect the bone formation which also in control of trabecular design structure. Over the time, the bone cells within the bone marrow will respond to the remodelling process and adapt to the induced mechanical loading to resist the loading and become stronger. Thus, the trabecular bone and marrow intimate interaction recommend that they both needed to be considered in parallel.

Most of the bone-related diseases were prone in involve elderly such as hip, wrist and spine fracture, required additional focus in understanding the biomechanics of bone. Due to the primary function of bone in withstand load during daily life activities, it is needed to understand the mechanical factors of bone. Improving understanding of bone metabolism and bone fracture aetiology is vital with the purpose of preventing fracture and identify the risk at an early stage. Therefore, the fluid-structure interaction between the bone marrow and trabecular bone need to be examined. With the purpose of understanding the bone marrow interaction between the trabecular bone and how it will have affected to mechanical properties, the finite element method was used. The simulation was designed to imitate real condition within trabecular bone during mechanical loading. These mechanical stimuli study may direct to the development of new approaches for enhancing bone healing while also help in preventing bone fracture. Therefore, current study might cover the following research questions;

1. How is the morphology of trabecular structure affecting the bone marrow characteristic.
2. How the orientation affects the local stress of trabecular structure and bone marrow flow properties at the tissue level.
3. What are the effects of morphology parameter indices correlation to the trabecular structure properties and bone marrow characteristics in physiological activity.
4. How the bone marrow within the structure contributes to trabecular bone strength.

1.3 Objective

This study is set out with the aim of assessing the importance on the interaction between the bone marrow and trabecular structure during physiological loading by using the FSI approach.

The specific objectives of this research are:

1. To determine the relationship of structure morphology and mechanical stimuli of bone marrow.
2. To investigate the effects of trabecular bone loading orientation to bone marrow characteristic.
3. To identify the flow characteristics of bone marrow with respect to the normal walking loading conditions as a daily physiological activity.
4. To determine the effect of bone marrow to the trabecular structure stiffness.

1.4 Scope of Study

This study concentrates on the fluid flow interaction within the trabecular bone of bovine femur. The bone marrow movements inside the trabecular bone were investigated in order to find out how it is affected by the bovine trabecular bone structure. Thus, the bone remodelling process behaviour from the bone marrow can be explored with the purpose of understanding the fluid characteristic phenomena. More specifically, the scope of this thesis study can be simplified as follow;

i. Idealise models were constructed based on parameters from literature review studies.

ii. The real samples of trabecular bone are harvested from the bovine femur.
iii. Different orientations are considered for the morphology study and the FSI analysis.
iv. All harvested bovine specimens are scanned using high-resolution micro-CT scanner (Skyscan1172).
v. The scanning data were then being studied by using the ImageJ software for morphology study.
vi. The morphology parameters, such as trabecular thickness, trabecular separation, trabecular number, volume fraction, connectivity, Mean Intercept Length (MIL) and Structure Model Index (SMI) are obtained from the ImageJ software.
vii. The morphology data are compared with the previous study from the literature.
viii. The scanning images were constructed to three-dimensional (3D) images by using Mimics software.
ix. From the 3D images, the models of the trabecular bone structure are imported into the Comsol software for analysis.
x. Load and boundary conditions are applied to the trabecular structure with bone marrow surrounding the trabecular model.
xi. The movement of the bone marrow are studied while the different load applied such as uniaxial load and gait loading based on normal physiological activity.
xii. The relationship between morphology parameters of bovine trabecular bone and physical activities with bone marrow characteristics were determined.

1.5 Significant of Finding

Trabecular bone consists of a hierarchical complex structure which constantly changing under certain factors of mechanical and chemical. These structures of trabecular bone play the main role in the distribution of stress in the skeletal system. By the time, the bone will lose its mass, and the structure will experience deterioration [7]. As a result, the bone becomes fragile, and its structure might break. This condition called as osteoporosis disease. More than 8.9 million fractures were caused by osteoporosis annually [8] and in fact, 1 in 5 men and 1 in 3 women aged over 50, will experience osteoporotic fractures [9]. In the year 2000, 9 million of new osteoporotic fracture were estimated [10], and by the year 2050, the occurrence of hip fracture will increase by 240% to 310% [11]. Studies from previous research have consistently found that treatments can reduce the risk of osteoporotic fracture depending on the patients' population and drug used [12, 13]. However, with the bone remodelling process and adequate nutrient transport within the bone, the osteoporotic fracture can be prevented.

The key to bone health that can prevent bone fractures is the mechanism which involves bone loss and formations of new bone called bone remodelling. Undoubtedly, bone remodelling process also requires adequate nutrient transport through the bone cells. Amazingly the bone can heal itself when there is external loads act upon the cells which can trigger the signals to the bones and start building themselves up. These loads come from human daily life activities which also include house chores, daily walking, and sports activity. Then again, the loads from human daily life will lead to the movement of the bone marrow within the trabecular structure which will cause the shear stress. This shear stress is one of the factors which trigger the bone cells to start the bone remodelling process. The capability of remodelling its structure and mass in adapting to biomechanical loading in daily life activities brand the bone as the highly efficient material.

Since the osteoporotic fractures are one of the health burdens which causes impairment, morbidity, mortality and decreases the quality of life in elderly, it is vital to increase understanding on how the bone cells mechanical stimuli actually works. Moreover, the previous study only focusing on the bone material properties itself while overlooking the functions of bone marrow within the trabecular structures [14-18]. Therefore, the present study was focusing on quantification of the trabecular bone behaviour with a presence of bone marrow to improve the accuracy and validity of trabecular failure and prediction of the bone remodelling process, which was failed to be submitted by previous assessments. Moreover, accurate bone remodelling process through the bone cell was predicted by using the FSI approach. Subsequently, this study will contribute to the future development of strategies towards enhancing the bone healing process and osteoporotic fracture preventions.

1.6 Thesis Structure and Organisation

Chapter 1 presents an introduction to this research which provides an overview and the importance of FSI in the trabecular bone study. It consists of a background of study, problem statement, objective, scope and significance of this research. Then, continue with Chapter 2 is the literature review which contains review on bone, trabecular bone, bone remodelling process and FSI in the trabecular bone application based on study of previous researchers. Chapter 3 explain on what steps used to complete this research. Starts from model developments for the simulation purpose, morphological study of trabecular sample, Finite Element Analysis (FEA), results validation to the statistical analysis. The results and discussions were delivered in Chapter 4 which is divided into five main sections; the morphology indices on the trabecular bone model, behaviour of bone marrow towards physical structure, FSI modelling of bone marrow through trabecular bone under uniaxial compression, trabecular bone mechanic of gait loading with a presence of bone marrow, and the effect of bone marrow within the trabecular structure by comparing between multiphysics and single approach. Lastly, Chapter 5 concludes the findings accomplished in this study. The limitations and recommendations also are highlight for future works.

REFERENCES

1. Anderson, C. (1994). Bone histomorphometry. *Bone and Mineral,* 26(2), p. 191.
2. Pal, S. (2014). *Mechanical properties of biological materials*, in. *Design of Artificial Human Joints & Organs*.(p. 23-40). Springer.
3. Keaveny, T.M., E.F. Morgan, and O. C.Yeh (2009). *BONE MECHANICS*, in. *BIOMEDICAL ENGINEERING AND DESIGN HANDBOOK*. The McGraw-Hill.
4. Nigg, B.M., B.R. MacIntosh, and J. Mester (2000). *Biomechanics and Biology of Movement*. (1st ed): Human Kinetics.
5. Laouira, A., et al. (2015). On the influence of marrow on the mechanical behavior of porcine trabecular bone under dynamic loading: a numerical investigation. *Computer Methods in Biomechanics and Biomedical Engineering*, p. 1-2.
6. Birmingham, E., et al. (2013). Computational Modelling of the Mechanics of Trabecular Bone and Marrow Using Fluid Structure Interaction Techniques. *Annals of Biomedical Engineering,* 41(4), p. 814-826.
7. Demontiero, O., C. Vidal, and G. Duque (2012). Aging and bone loss: new insights for the clinician. *Therapeutic Advances in Musculoskeletal Disease,* 4(2), p. 61-76.
8. Pisani, P., et al. (2016). Major osteoporotic fragility fractures: Risk factor updates and societal impact. *World Journal of Orthopedics,* 7(3), p. 171-181.
9. Kanis, J.A., et al. (2000). Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int,* 11(8), p. 669-74.
10. Johnell, O. and J.A. Kanis (2006). An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis International,* 17(12), p. 1726-1733.
11. Kanis, J.A. (2002). Diagnosis of osteoporosis and assessment of fracture risk. *Lancet,* 359(9321), p. 1929-36.

12. Kanis, J.A., et al. (2013). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int,* 24(1), p. 23-57.

13. Black , D.M., et al. (2007). Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *New England Journal of Medicine,* 356(18), p. 1809-1822.

14. Lindahl, O. (1976). Mechanical properties of dried defatted spongy bone. *Acta Orthopaedica Scandinavica,* 47(1), p. 11-19.

15. Lewis, J. (1982). Properties and an anisotropic model of cancellous bone from the proximal tibial epiphysis. *Journal of biomechanical engineering,* 104, p. 50-56.

16. Chevalier, Y., et al. (2007). Validation of a voxel-based FE method for prediction of the uniaxial apparent modulus of human trabecular bone using macroscopic mechanical tests and nanoindentation. *Journal of Biomechanics,* 40(15), p. 3333-3340.

17. Gong, H., M. Zhang, and Y. Fan (2011). Micro-finite element analysis of trabecular bone yield behavior—effects of tissue nonlinear material properties. *Journal of Mechanics in Medicine and Biology,* 11(03), p. 563-580.

18. Fatihhi, S.J., et al. (2016). Effect of torsional loading on compressive fatigue behaviour of trabecular bone. *Journal of the Mechanical Behavior of Biomedical Materials,* 54, p. 21-32.

19. Bach, R.B., D.B. Burr, and N.A. Sharkey (2010). *Skeletal Tissue Mechanics*: Springer New York.

20. Samuel, S.P., G.R. Baran, Y. Wei, and B.L. Davis (2009). *Biomechanics - Part II*, in J.S. Khurana, Editor. *Bone Pathology*.(p. 69-77). Humana Press: Totowa, NJ.

21. Wolff, J., P. Maquet, and R. Furlong (1986). *The law of bone remodelling*: Springer-Verlag.

22. Khurana, J.S. (2009). *Bone Pathology*: Humana Press.

23. Biewener, A.A., N.L. Fazzalari, D.D. Konieczynski, and R.V. Baudinette (1996). Adaptive changes in trabecular architecture in relation to functional strain patterns and disuse. *Bone,* 19(1), p. 1-8.

24. Parfitt, A.M. (1993). Morphometry of bone resorption: Introduction and overview. *Bone,* 14(3), p. 435-441.

25. Keaveny, T.M. and W.C. Hayes (1993). Mechanical properties of cortical and trabecular bone. *Bone,* 7, p. 285-344.

26. Keaveny, T.M., E.F. Morgan, G.L. Niebur, and O.C. Yeh (2001). Biomechanics of trabecular bone. *Annu Rev Biomed Eng,* 3, p. 307-33.

27. Hodgskinson, R. and J.D. Currey (1993). Separate effects of osteoporosis and density on the strength and stiffness of human cancellous bone. *Clinical Biomechanics,* 8(5), p. 262-268.

28. Morgan, E.F., O.C. Yeh, W.C. Chang, and T.M. Keaveny (2001). Nonlinear behavior of trabecular bone at small strains. *J Biomech Eng,* 123(1), p. 1-9.

29. Carter, D.R. and W.C. Hayes (1977). The compressive behavior of bone as a two-phase porous structure. *J Bone Joint Surg Am,* 59(7), p. 954-62.

30. McCalden, R.W., J.A. McGeough, and C.M. Court-Brown (1997). Age-Related Changes in the Compressive Strength of Cancellous Bone. The Relative Importance of Changes in Density and Trabecular Architecture*. *The Journal of Bone & Joint Surgery,* 79(3), p. 421-7.

31. Ouyang, J., et al. (1997). Biomechanical characteristics of human trabecular bone. *Clinical Biomechanics,* 12(7–8), p. 522-524.

32. Shi, X., et al. (2010). Effects of trabecular type and orientation on microdamage susceptibility in trabecular bone. *Bone,* 46(5), p. 1260-6.

33. Shi, X., X. Wang, and G. Niebur (2009). Effects of Loading Orientation on the Morphology of the Predicted Yielded Regions in Trabecular Bone. *Annals of Biomedical Engineering,* 37(2), p. 354-362.

34. Brennan, O., et al. (2009). Biomechanical properties across trabeculae from the proximal femur of normal and ovariectomised sheep. *J Biomech,* 42(4), p. 498-503.

35. Verhulp, E., B. van Rietbergen, R. Müller, and R. Huiskes (2008). Indirect determination of trabecular bone effective tissue failure properties using micro-finite element simulations. *Journal of Biomechanics,* 41(7), p. 1479-1485.

36. Bayraktar, H.H., et al. (2004). Comparison of the elastic and yield properties of human femoral trabecular and cortical bone tissue. *Journal of Biomechanics,* 37(1), p. 27-35.

37. Morgan, E.F., H.H. Bayraktar, and T.M. Keaveny (2003). Trabecular bone modulus–density relationships depend on anatomic site. *Journal of Biomechanics,* 36(7), p. 897-904.

38. Homminga, J., et al. (2002). Cancellous bone mechanical properties from normals and patients with hip fractures differ on the structure level, not on the bone hard tissue level. *Bone,* 30(5), p. 759-764.

39. Hoffler, C.E., et al. (2000). Heterogeneity of bone lamellar-level elastic moduli. *Bone,* 26(6), p. 603-609.

40. Niebur, G.L., et al. (2000). High-resolution finite element models with tissue strength asymmetry accurately predict failure of trabecular bone. *J Biomech,* 33(12), p. 1575-83.

41. Turner, C.H., et al. (1999). The elastic properties of trabecular and cortical bone tissues are similar: results from two microscopic measurement techniques. *Journal of Biomechanics,* 32(4), p. 437-441.

42. Zysset, P.K., et al. (1999). Elastic modulus and hardness of cortical and trabecular bone lamellae measured by nanoindentation in the human femur. *Journal of Biomechanics,* 32(10), p. 1005-1012.

43. Rho, J.Y., M.E. Roy, T.Y. Tsui, and G.M. Pharr (1999). Elastic properties of microstructural components of human bone tissue as measured by nanoindentation. *Journal of biomedical materials research,* 45(1), p. 48-54.

44. Ladd, A.J., J.H. Kinney, D.L. Haupt, and S.A. Goldstein (1998). Finite-element modeling of trabecular bone: comparison with mechanical testing and determination of tissue modulus. *J Orthop Res,* 16(5), p. 622-8.

45. Hou, F.J., et al. (1998). Human vertebral body apparent and hard tissue stiffness. *Journal of biomechanics,* 31(11), p. 1009-1015.

46. Nicholson, P.H.F., et al. (1997). Structural and material mechanical properties of human vertebral cancellous bone. *Medical Engineering & Physics,* 19(8), p. 729-737.

47. Roy, M., J.-Y. Rho, T.Y. Tsui, and G.M. Pharr (1996). Variation of Young's modulus and hardness in human lumbar vertebrae measured by nanoindentation. *ASME-PUBLICATIONS-BED,* 33, p. 385-386.

48. Ko, C.-C., W.H. Douglas, and Y.-S. Cheng (1995). Intrinsic mechanical competence of cortical and trabecular bone measured by nanoindentation and microindentation probes. *ASME-PUBLICATIONS-BED,* 29, p. 415-415.

49. Rho, J.Y., R.B. Ashman, and C.H. Turner (1993). Young's modulus of trabecular and cortical bone material: ultrasonic and microtensile measurements. *Journal of biomechanics,* 26(2), p. 111-119.

50. Ashman, R.B. and R. Jae Young (1988). Elastic modulus of trabecular bone material. *Journal of Biomechanics,* 21(3), p. 177-181.

51. Townsend, P.R., R.M. Rose, and E.L. Radin (1975). Buckling studies of single human trabeculae. *Journal of Biomechanics,* 8(3), p. 199-201.

52. Rietbergen, v.B. and H. Huiskes (2001). *Elastic constants of cancellous bone*, in. *Bone mechanics handbook / Ed. S.C. Cowin.*(p. 15/1 - null). CRC Press: London.

53. Van Eijden, T., L. Van Ruijven, and E. Giesen (2004). Bone tissue stiffness in the mandibular condyle is dependent on the direction and density of the cancellous structure. *Calcified Tissue International,* 75(6), p. 502-508.

54. O'Mahony, A.M., J.L. Williams, J.O. Katz, and P. Spencer (2000). Anisotropic elastic properties of cancellous bone from a human edentulous mandible. *Clinical oral implants research,* 11(5), p. 415-421.

55. Misch, C.E., Z. Qu, and M.W. Bidez (1999). Mechanical properties of trabecular bone in the human mandible: implications for dental implant treatment planning and surgical placement. *J Oral Maxillofac Surg,* 57(6), p. 700-6; discussion 706-8.

56. Keaveny, T.M., et al. (1997). Systematic and random errors in compression testing of trabecular bone. *J Orthop Res,* 15(1), p. 101-10.

57. Linde, F. (1994). Elastic and viscoelastic properties of trabecular bone by a compression testing approach. *Dan Med Bull,* 41(2), p. 119-38.

58. Odgaard, A. and F. Linde (1991). The underestimation of Young's modulus in compressive testing of cancellous bone specimens. *Journal of Biomechanics,* 24(8), p. 691-698.

59. Struhl, S., et al. (1987). The distribution of mechanical properties of trabecular bone within vertebral bodies and iliac crest: correlation with computed tomography density. *Trans Orthop Res Soc,* 262.

60. Keller, T.S., et al. (1989). Regional Variations in the Compressive Properties of Lumbar Vertebral Trabeculae: Effects of Disc Degeneration. *Spine,* 14(9), p. 1012-1019.

61. Ciarelli, M., et al. (1986). Experimental determination of the orthogonal mechanical properties, density, and distribution of human trabecular bone from the major metaphyseal regions utilizing materials testing and computed tomography. *Trans Orthop Res Soc,* 42.

62. Martens, M., et al. (1983). The mechanical characteristics of cancellous bone at the upper femoral region. *Journal of Biomechanics,* 16(12), p. 971-983.

63. Goldstein, S.A. (1987). The mechanical properties of trabecular bone: Dependence on anatomic location and function. *Journal of Biomechanics,* 20(11–12), p. 1055-1061.

64. Brown, T.D. and A.B. Ferguson (1980). Mechanical property distributions in the cancellous bone of the human proximal femur. *Acta Orthopaedica Scandinavica,* 51(1-6), p. 429-437.

65. Pugh, J.W., R.M. Rose, and E.L. Radin (1973). Elastic and viscoelastic properties of trabecular bone: dependence on structure. *Journal of biomechanics,* 6(5), p. 475IN7479-478485.

66. McElhaney, J.H., et al. (1970). Mechanical properties of cranial bone. *Journal of biomechanics,* 3(5), p. 495IN5497-496511.

67. Hildebrand, T., et al. (1999). Direct three-dimensional morphometric analysis of human cancellous bone: Microstructural data from spine, femur, iliac crest, and calcaneus. *Journal of Bone and Mineral Research,* 14(7), p. 1167-1174.

68. Mulder, L., J.H. Koolstra, H.W. de Jonge, and T. van Eijden (2006). Architecture and mineralization of developing cortical and trabecular bone of the mandible. *Anatomy and Embryology,* 211(1), p. 71-78.

69. A M Parfitt, C.H.M., A R Villanueva, M Kleerekoper, B Frame, D S Rao (1983). Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. *J. Clin. Invest.,* (72), p. 1396–1409.

70. Currey, J. (2012). The structure and mechanics of bone. *Journal of Materials Science,* 47(1), p. 41-54.

71. Kazama, J.J., et al. (2010). Cancellous Bone Volume Is an Indicator for Trabecular Bone Connectivity in Dialysis Patients. *Clinical Journal of the American Society of Nephrology,* 5(2), p. 292-298.

72. Zhang, Z.M., et al. (2010). Micro-CT and mechanical evaluation of subchondral trabecular bone structure between postmenopausal women with osteoarthritis and osteoporosis. *Osteoporosis International,* 21(8), p. 1383-1390.

73. Crawford, R.P., C.E. Cann, and T.M. Keaveny (2003). Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone,* 33(4), p. 744-750.

74. Krischak, G.D., et al. (1999). Predictive value of bone mineral density and Singh Index for the in vitro mechanical properties of cancellous bone in the femoral head. *Clinical Biomechanics,* 14(5), p. 346-351.

75. Hildebrand, T. and P. Rüegsegger (1997). A new method for the model-independent assessment of thickness in three-dimensional images. *Journal of Microscopy,* 185(1), p. 67-75.

76. Anderson, I.A. and J.B. Carman (2000). How do changes to plate thickness, length, and face-connectivity affect femoral cancellous bone's density and surface area? An investigation using regular cellular models. *Journal of Biomechanics,* 33(3), p. 327-335.

77. Parfitt, A.M., C.H.E. Mathews, and A.B. Villanueva (1983). Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. *Journal of Clinical Investigation,* 72(4), p. 1396-1409.

78. Kothari, M., et al. (1999). Measurement of intraspecimen variations in vertebral cancellous bone architecture. *Bone,* 25(2), p. 245-50.

79. Teo, J.C.M., K.M. Si-Hoe, J.E.L. Keh, and S.H. Teoh (2007). Correlation of cancellous bone microarchitectural parameters from microCT to CT number and bone mechanical properties. *Materials Science and Engineering: C,* 27(2), p. 333-339.

80. van Lenthe, G.H. and R. Huiskes (2002). How morphology predicts mechanical properties of trabecular structures depends on intra-specimen trabecular thickness variations. *Journal of Biomechanics,* 35(9), p. 1191-1197.

81. Whitehouse, W.J. (1974). The quantitative morphology of anisotropic trabecular bone. *J Microsc,* 101(Pt 2), p. 153-68.

82. Raux, P., et al. (1975). Trabecular architecture of the human patella. *Journal of Biomechanics,* 8(1), p. 1-7.

83. Cowin, S.C. (2001). *Bone Mechanics Handbook, Second Edition*: CRC Press.

84. Majumdar, S., et al. (1998). High-Resolution Magnetic Resonance Imaging: Three-Dimensional Trabecular Bone Architecture and Biomechanical Properties. *Bone,* 22(5), p. 445-454.

85. Rho, J.Y., M.C. Hobatho, and R.B. Ashman (1995). Relations of mechanical properties to density and CT numbers in human bone. *Medical Engineering & Physics,* 17(5), p. 347-355.

86. Morgan, E.F., et al. (2004). Contribution of inter-site variations in architecture to trabecular bone apparent yield strains. *Journal of Biomechanics,* 37(9), p. 1413-1420.

87. Nicholson, P.H.F., et al. (1998). Do quantitative ultrasound measurements reflect structure independently of density in human vertebral cancellous bone? *Bone,* 23(5), p. 425-431.

88. Portero-Muzy, N., et al. (2007). Eulerstrut.cavity, a New Histomorphometric Parameter of Connectivity Reflects Bone Strength and Speed of Sound in Trabecular Bone from Human Os Calcis. *Calcified Tissue International,* 81(2), p. 92-98.

89. Yeni, Y.N., et al. (2008). Trabecular shear stress amplification and variability in human vertebral cancellous bone: Relationship with age, gender, spine level and trabecular architecture. *Bone,* 42(3), p. 591-596.

90. Kreipke, T.C. and G.L. Niebur (2017). Anisotropic Permeability of Trabecular Bone and its Relationship to Fabric and Architecture: A Computational Study. *Annals of Biomedical Engineering,* 45(6), p. 1543-1554.

91. Sandino, C., D.D. McErlain, J. Schipilow, and S.K. Boyd (2017). Mechanical stimuli of trabecular bone in osteoporosis: A numerical simulation by finite element analysis of microarchitecture. *Journal of the Mechanical Behavior of Biomedical Materials,* 66, p. 19-27.

92. Linde, F., et al. (1991). Mechanical properties of trabecular bone. Dependency on strain rate. *Journal of Biomechanics,* 24(9), p. 803-809.

93. Yao, X., P. Wang, R. Dai, and H. Yeh (2010). Microstructures and properties of cancellous bone of avascular necrosis of femoral heads. *Acta Mechanica Sinica,* 26(1), p. 13-19.

94. Teng, S. and S.W. Herring (1995). A stereological study of trabecular architecture in the mandibular condyle of the pig. *Archives of Oral Biology,* 40(4), p. 299-310.

95. Mulder, L., L.J. van Ruijven, J.H. Koolstra, and T.M.G.J. van Eijden (2007). Biomechanical consequences of developmental changes in trabecular architecture and mineralization of the pig mandibular condyle. *Journal of Biomechanics,* 40(7), p. 1575-1582.

96. Haapasalo, H., et al. (2000). Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. *Bone,* 27(3), p. 351-357.

97. Burt, L.A., J.D. Schipilow, and S.K. Boyd (2016). Competitive trampolining influences trabecular bone structure, bone size, and bone strength. *Journal of Sport and Health Science,* 5(4), p. 469-475.

98. Iura, A., et al. (2015). Mechanical Loading Synergistically Increases Trabecular Bone Volume and Improves Mechanical Properties in the Mouse when BMP Signaling Is Specifically Ablated in Osteoblasts. *PLOS ONE,* 10(10), p. e0141345.

99. Ciarelli, T.E., D.P. Fyhrie, M.B. Schaffler, and S.A. Goldstein (2000). Variations in Three-Dimensional Cancellous Bone Architecture of the Proximal Femur in Female Hip Fractures and in Controls. *Journal of Bone and Mineral Research,* 15(1), p. 32-40.

100. Qiu, S., D.S. Rao, S. Palnitkar, and A.M. Parfitt (2003). Reduced Iliac Cancellous Osteocyte Density in Patients With Osteoporotic Vertebral Fracture. *Journal of Bone and Mineral Research,* 18(9), p. 1657-1663.

101. Dempster, D.W., et al. (2007). Preserved three-dimensional cancellous bone structure in mild primary hyperparathyroidism. *Bone,* 41(1), p. 19-24.

102. Chen, H., S. Shoumura, S. Emura, and Y. Bunai (2008). Regional variations of vertebral trabecular bone microstructure with age and gender. *Osteoporosis International,* 19(10), p. 1473-1483.

103. Djuric, M., et al. (2010). Region-Specific Sex-Dependent Pattern of Age-Related Changes of Proximal Femoral Cancellous Bone and Its Implications on Differential Bone Fragility. *Calcified Tissue International,* 86(3), p. 192-201.

104. Tracy, J., et al. (2006). Racial differences in the prevalence of vertebral fractures in older men: the Baltimore Men's Osteoporosis Study. *Osteoporosis International,* 17(1), p. 99-104.

105. Gilsanz, V., et al. (1998). Differential Effect of Race on the Axial and Appendicular Skeletons of Children. *The Journal of Clinical Endocrinology & Metabolism,* 83(5), p. 1420-1427.

106. Piney, A. (1922). The Anatomy of the Bone Marrow: With Special Reference to the Distribution of the Red Marrow. *The British Medical Journal,* 2(3226), p. 792-795.

107. Vande Berg, B.C., J. Malghem, F.E. Lecouvet, and B. Maldague (1998). Magnetic resonance imaging of the normal bone marrow. *Skeletal Radiology,* 27(9), p. 471-483.

108. Gimble, J.M., C.E. Robinson, X. Wu, and K.A. Kelly (1996). The function of adipocytes in the bone marrow stroma: an update. *Bone,* 19(5), p. 421-428.

109. Kafka, V. (1993). On hydraulic strengthening of bones. *Biorheology,* 20(6), p. 789-93.

110. Ochoa, J.A., et al. (1997). In vivo observations of hydraulic stiffenino in the canine fernoral head. *Journal of Biomechanical Engineering,* 119(1), p. 103-108.

111. Haider, I.T., A.D. Speirs, and H. Frei (2013). Effect of boundary conditions, impact loading and hydraulic stiffening on femoral fracture strength. *J Biomech,* 46(13), p. 2115-21.

112. Liebschner, M.A.K. and T.S. Keller (2005). Hydraulic Strengthening Affects the Stiffness and Strength of Cortical Bone. *Annals of Biomedical Engineering,* 33(1), p. 26-38.

113. Laming, E., et al. (2012). Demonstration of early functional compromise of bone marrow derived hematopoietic progenitor cells during bovine neonatal pancytopenia through in vitro culture of bone marrow biopsies. *BMC Research Notes,* 5, p. 599-599.

114. Yourek, G., S.M. McCormick, J.J. Mao, and G.C. Reilly (2010). Shear stress induces osteogenic differentiation of human mesenchymal stem cells. *Regen Med,* 5(5), p. 713-24.

115. Ochoa, I., et al. (2009). Permeability evaluation of 45S5 Bioglass®-based scaffolds for bone tissue engineering. *Journal of Biomechanics,* 42(3), p. 257-260.

116. Gurkan, U. and O. Akkus (2008). The Mechanical Environment of Bone Marrow: A Review. *Annals of Biomedical Engineering,* 36(12), p. 1978-1991.

117. Owan, I., et al. (1997). Mechanotransduction in bone: osteoblasts are more responsive to fluid forces than mechanical strain. *American Journal of Physiology - Cell Physiology,* 273(3), p. C810-C815.

118. You, J., et al. (2000). Substrate Deformation Levels Associated With Routine Physical Activity Are Less Stimulatory to Bone Cells Relative to Loading-Induced Oscillatory Fluid Flow. *Journal of Biomechanical Engineering,* 122(4), p. 387-393.

119. Tsuchiya, N., D. Kodama, S. Goto, and A. Togari (2015). Shear stress-induced Ca2+ elevation is mediated by autocrine-acting glutamate in osteoblastic MC3T3-E1 cells. *Journal of Pharmacological Sciences,* 127(3), p. 311-318.

120. Karande, T.S., J.L. Ong, and C.M. Agrawal (2004). Diffusion in musculoskeletal tissue engineering scaffolds: design issues related to porosity, permeability, architecture, and nutrient mixing. *Annals of biomedical engineering,* 32(12), p. 1728-1743.

121. Yu, X., et al. (2004). Bioreactor-based bone tissue engineering: the influence of dynamic flow on osteoblast phenotypic expression and matrix mineralization. *Proceedings of the National Academy of Sciences of the United States of America,* 101(31), p. 11203-11208.

122. Syahrom, A., M.R. Abdul Kadir, M.N. Harun, and A. Öchsner (2015). Permeability study of cancellous bone and its idealised structures. *Medical Engineering & Physics,* 37(1), p. 77-86.

123. Widmer, R.P. and S.J. Ferguson (2013). A comparison and verification of computational methods to determine the permeability of vertebral trabecular

bone. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine,* 227(6), p. 617-628.

124. Daish, C., et al. (2017). Estimation of anisotropic permeability in trabecular bone based on microCT imaging and pore-scale fluid dynamics simulations. *Bone Reports,* 6, p. 129-139.

125. Zhang, Z., et al. (2013). Hierarchical tailoring of strut architecture to control permeability of additive manufactured titanium implants. *Materials Science and Engineering: C,* 33(7), p. 4055-4062.

126. Nauman, E.A., K.E. Fong, and T.M. Keaveny (1999). Dependence of Intertrabecular Permeability on Flow Direction and Anatomic Site. *Annals of Biomedical Engineering,* 27(4), p. 517-524.

127. Coughlin, T.R. and G.L. Niebur (2012). Fluid shear stress in trabecular bone marrow due to low-magnitude high-frequency vibration. *Journal of Biomechanics,* 45(13), p. 2222-2229.

128. Syahrom, A., M.R. Abdul Kadir, J. Abdullah, and A. Öchsner (2012). Permeability studies of artificial and natural cancellous bone structures. *Medical Engineering & Physics,* (0).

129. Baroud, G., et al. (2004). Experimental and theoretical investigation of directional permeability of human vertebral cancellous bone for cement infiltration. *Journal of Biomechanics,* 37(2), p. 189-196.

130. Sander, E.A., D.A. Shimko, K.C. Dee, and E.A. Nauman (2003). Examination of continuum and micro-structural properties of human vertebral cancellous bone using combined cellular solid models. *Biomechanics and Modeling in Mechanobiology,* 2(2), p. 97-107.

131. Kohles, S.S., et al. (2001). Direct perfusion measurements of cancellous bone anisotropic permeability. *Journal of Biomechanics,* 34(9), p. 1197-1202.

132. Lim, T.-H. and J.H. Hong (2000). Poroelastic properties of bovine vertebral trabecular bone. *Journal of Orthopaedic Research,* 18(4), p. 671-677.

133. Grimm, M.J. and J.L. Williams (1997). Measurements of permeability in human calcaneal trabecular bone. *Journal of Biomechanics,* 30(7), p. 743-745.

134. Hui, P.W., P.C. Leung, and A. Sher (1996). Fluid conductance of cancellous bone graft as a predictor for graft-host interface healing. *Journal of Biomechanics,* 29(1), p. 123-132.

135. Wang, M.-K., et al. (2012). Different roles of TGF-β in the multi-lineage differentiation of stem cells. *World Journal of Stem Cells,* 4(5), p. 28-34.

136. Adachi, T., Y. Kameo, and M. Hojo (2010). Trabecular bone remodelling simulation considering osteocytic response to fluid-induced shear stress. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences,* 368(1920), p. 2669-2682.

137. McAllister, T.N. and J.A. Frangos (1999). Steady and Transient Fluid Shear Stress Stimulate NO Release in Osteoblasts Through Distinct Biochemical Pathways. *Journal of Bone and Mineral Research,* 14(6), p. 930-936.

138. Li, Y.J., et al. (2004). Oscillatory fluid flow affects human marrow stromal cell proliferation and differentiation. *J Orthop Res,* 22(6), p. 1283-9.

139. Nagatomi, J., et al. (2002). Effects of cyclic pressure on bone marrow cell cultures. *J Biomech Eng,* 124(3), p. 308-14.

140. Nagatomi, J., et al. (2003). Cyclic pressure affects osteoblast functions pertinent to osteogenesis. *Ann Biomed Eng,* 31(8), p. 917-23.

141. Qin, Y.-X., T. Kaplan, A. Saldanha, and C. Rubin (2003). Fluid pressure gradients, arising from oscillations in intramedullary pressure, is correlated with the formation of bone and inhibition of intracortical porosity. *Journal of Biomechanics,* 36(10), p. 1427-1437.

142. Rubin, J., C. Rubin, and C.R. Jacobs (2006). Molecular pathways mediating mechanical signaling in bone. *Gene,* 367, p. 1-16.

143. Liu, G.-Z., et al. (2001). Nitric oxide mediates the change of proteoglycan synthesis in the human lumbar intervertebral disc in response to hydrostatic pressure. *Spine,* 26(2), p. 134-141.

144. Aguirre, J., et al. (2001). Endothelial nitric oxide synthase gene-deficient mice demonstrate marked retardation in postnatal bone formation, reduced bone volume, and defects in osteoblast maturation and activity. *Am J Pathol,* 158(1), p. 247-57.

145. Wittkowske, C., G.C. Reilly, D. Lacroix, and C.M. Perrault (2016). In Vitro Bone Cell Models: Impact of Fluid Shear Stress on Bone Formation. *Frontiers in Bioengineering and Biotechnology,* 4, p. 87.

146. Parfitt, A.M., et al. (1996). A new model for the regulation of bone resorption, with particular reference to the effects of bisphosphonates. *J Bone Miner Res,* 11(2), p. 150-9.

147. Ott, S.M. (2002). *Chapter 19 - Histomorphometric Analysis of Bone Remodeling*, in P.B. John, et al., Editors. *Principles of Bone Biology (Second Edition)*.(p. 303-XXIII). Academic Press: San Diego.

148. Klein-Nulend, J., R.G. Bacabac, and A.D. Bakker (2012). Mechanical loading and how it affects bone cells: the role of the osteocyte cytoskeleton in maintaining our skeleton. *Eur Cell Mater,* 24, p. 278-91.

149. Klein-Nulend, J., et al. (1995). Sensitivity of osteocytes to biomechanical stress in vitro. *Faseb j,* 9(5), p. 441-5.

150. McNamara, L.M. and P.J. Prendergast (2007). Bone remodelling algorithms incorporating both strain and microdamage stimuli. *Journal of Biomechanics,* 40(6), p. 1381-1391.

151. Schnitzler, C.M. and J. Mesquita (1998). Bone Marrow Composition and Bone Microarchitecture and Turnover in Blacks and Whites. *Journal of Bone and Mineral Research,* 13(8), p. 1300-1307.

152. Rosen, C.J. and M.L. Bouxsein (2006). Mechanisms of Disease: is osteoporosis the obesity of bone? *Nat Clin Pract Rheum,* 2(1), p. 35-43.

153. Muruganandan, S. and C.J. Sinal (2014). The impact of bone marrow adipocytes on osteoblast and osteoclast differentiation. *IUBMB Life*.

154. Bryant, J.D. (1983). The effect of impact on the marrow pressure of long bones in vitro. *Journal of Biomechanics,* 16(8), p. 659-665.

155. Downey, D.J., P.A. Simkin, and R. Taggart, The effect of compressive loading on intraosseous pressure in the femoral head in vitro, in *The Journal of Bone & Joint Surgery*. 1988. p. 871-877.

156. Grellier, M., R. Bareille, C. Bourget, and J. Amédée (2009). Responsiveness of human bone marrow stromal cells to shear stress. *Journal of tissue engineering and regenerative medicine,* 3(4), p. 302-309.

157. Metzger, T.A., et al. (2015). Pressure and shear stress in trabecular bone marrow during whole bone loading. *Journal of Biomechanics,* 48(12), p. 3035-3043.

158. Letechipia, J.E., A. Alessi, G. Rodriguez, and J. Asbun (2010). Would increased interstitial fluid flow through in situ mechanical stimulation enhance bone remodeling? *Medical Hypotheses,* 75(2), p. 196-198.

159. Hillsley, M.V. and J.A. Frangos (1994). Review: Bone tissue engineering: The role of interstitial fluid flow. *Biotechnology and Bioengineering,* 43(7), p. 573-581.

160. Oñate, E. (2009). *Introduction to the Finite Element Method for Structural Analysis*, in. *Structural Analysis with the Finite Element Method: Linear Statics*.(p. 1-42). Springer Netherlands: Dordrecht.

161. Cook, R.D. (1995). *Finite element modeling for stress analysis*: Wiley.

162. Fish, J. and T. Belytschko (2007). *A First Course in Finite Elements*: Wiley.

163. Zuo, J., et al. (2008). Reproducibility of the quantitative assessment of cartilage morphology and trabecular bone structure with magnetic resonance imaging at 7 T. *Magnetic Resonance Imaging,* 26(4), p. 560-566.

164. Niebur, G.L., J.C. Yuen, A.C. Hsia, and T.M. Keaveny (1999). Convergence behavior of high-resolution finite element models of trabecular bone. *J Biomech Eng,* 121(6), p. 629-35.

165. Kim, D.-G., et al. (2004). The effect of microcomputed tomography scanning and reconstruction voxel size on the accuracy of stereological measurements in human cancellous bone. *Bone,* 35(6), p. 1375-1382.

166. Leung, S.Y., M. Browne, and A.M. New (2008). Smooth surface micro finite element modelling of a cancellous bone analogue material. *Proc Inst Mech Eng H,* 222(1), p. 145-9.

167. Sandino, C., P. Kroliczek, D.D. McErlain, and S.K. Boyd (2014). Predicting the permeability of trabecular bone by micro-computed tomography and finite element modeling. *J Biomech,* 47(12), p. 3129-34.

168. Fatihhi, S.J., et al. (2015). Uniaxial and Multiaxial Fatigue Life Prediction of the Trabecular Bone Based on Physiological Loading: A Comparative Study. *Annals of Biomedical Engineering,* 43(10), p. 2487-2502.

169. Sanyal, A., et al. (2012). Shear strength behavior of human trabecular bone. *J Biomech,* 45(15), p. 2513-9.

170. Parr, W.C.H., et al. (2013). Finite element micro-modelling of a human ankle bone reveals the importance of the trabecular network to mechanical performance: New methods for the generation and comparison of 3D models. *Journal of Biomechanics,* 46(1), p. 200-205.

171. Van Rietbergen, B., R. Huiskes, F. Eckstein, and P. Ruegsegger (2003). Trabecular bone tissue strains in the healthy and osteoporotic human femur. *J Bone Miner Res,* 18(10), p. 1781-8.

172. Kroyer, R. (2003). FSI analysis in supersonic fluid flow. *Computers & Structures,* 81(8–11), p. 755-764.

173. Korobenko, A., et al. (2013). Structural Mechanics Modeling and FSI Simulation of Wind Turbines. *Mathematical Models and Methods in Applied Sciences,* 23(02), p. 249-272.

174. Coulombe-Pontbriand, P. and M. Nahon (2009). Experimental testing and modeling of a tethered spherical aerostat in an outdoor environment. *Journal of Wind Engineering and Industrial Aerodynamics,* 97(5–6), p. 208-218.

175. Liu, Z.G., Y. Liu, and J. Lu (2012). Numerical simulation of the fluid–structure interaction for an elastic cylinder subjected to tubular fluid flow. *Computers & Fluids,* 68(0), p. 192-202.

176. Bertram, C.D. (2008). Flow-induced oscillation of collapsed tubes and airway structures. *Respiratory Physiology & Neurobiology,* 163(1–3), p. 256-265.

177. Sugiura, S., et al. (2012). Multi-scale simulations of cardiac electrophysiology and mechanics using the University of Tokyo heart simulator. *Progress in Biophysics and Molecular Biology,* 110(2–3), p. 380-389.

178. Chui, Y.-P. and P.-A. Heng (2010). A meshless rheological model for blood-vessel interaction in endovascular simulation. *Progress in Biophysics and Molecular Biology,* 103(2–3), p. 252-261.

179. Kapellos, G.E., T.S. Alexiou, and A.C. Payatakes (2010). Theoretical modeling of fluid flow in cellular biological media: An overview. *Mathematical Biosciences,* 225(2), p. 83-93.

180. Olson, S.D., S.S. Suarez, and L.J. Fauci (2011). Coupling biochemistry and hydrodynamics captures hyperactivated sperm motility in a simple flagellar model. *Journal of Theoretical Biology,* 283(1), p. 203-216.

181. Szczerba, D., H. Kurz, and G. Szekely (2009). A computational model of intussusceptive microvascular growth and remodeling. *Journal of Theoretical Biology,* 261(4), p. 570-583.

182. Axisa, F. and J. Antunes (2007). *Chapter 1 Introduction to fluid-structure coupling*, in A. François and A. Jose, Editors. *Modelling of Mechanical Systems*.(p. 1-44). Butterworth-Heinemann.

183. Hou, G., J. Wang, and A. Layton (2012). Numerical Methods for Fluid-Structure Interaction — A Review. *Communications in Computational Physics,* 12(2), p. 337-377.

184. Hirsch, C. (1951). Studies on the Mechanism of Low Back Pain. *Acta Orthopaedica Scandinavica,* 20(4), p. 261-274.

185. BROWN, T., R.J. HANSEN, and A.J. YORRA (1957). Some Mechanical Tests on the Lumbosacral Spine with Particular Reference to the Intervertebral Discs. *A Preliminary Report,* 39(5), p. 1135-1164.

186. Swanson, S.A.V. and M.A.R. Freeman (1966). Is bone hydraulically strengthened? *Medical and biological engineering,* 4(5), p. 433-438.

187. Ochoa, J.A., A.P. Sanders, D.A. Heck, and B.M. Hillberry (1991). Stiffening of the femoral head due to intertrabecular fluid and intraosseous pressure. *Journal of Biomechanical Engineering,* 113(3), p. 259-262.

188. Petrella, A.J. and B. Hillberry. (*1996).* in An in vitro study of hydraulic stiffening in cancellous bone. *Biomedical Engineering Conference, 1996., Proceedings of the 1996 Fifteenth Southern*.317-318.

189. Metzger, T.A., et al. (2015). The In Situ Mechanics of Trabecular Bone Marrow: The Potential for Mechanobiological Response. *Journal of Biomechanical Engineering,* 137(1), p. 011006-011006.

190. Birmingham, E., G.L. Niebur, L.M. McNamara, and P.E. McHugh (2015). An Experimental and Computational Investigation of Bone Formation in Mechanically Loaded Trabecular Bone Explants. *Annals of Biomedical Engineering*, p. 1-13.

191. Zhao, F., T. Vaughan, and L. McNamara (2015). Quantification of fluid shear stress in bone tissue engineering scaffolds with spherical and cubical pore architectures. *Biomechanics and Modeling in Mechanobiology*, p. 1-17.

192. Nik, A.B. and B. Vahidi. (*2015).* in The effect of bone scaffold gradient architecture design on stem cell mechanical modulation: a computational study. *2015 22nd Iranian Conference on Biomedical Engineering (ICBME)*.309-313.

193. Syahrom, A., M.R.A. Kadir, J. Abdullah, and A. Ochsner (2011). Mechanical and microarchitectural analyses of cancellous bone through experiment and computer simulation. *Medical & Biological Engineering & Computing,* 49(12), p. 1393-1403.

194. Doube, M., et al. (2010). BoneJ: Free and extensible bone image analysis in ImageJ. *Bone,* 47(6), p. 1076-1079.

195. Bergmann, G., et al. (2001). Hip contact forces and gait patterns from routine activities. *Journal of Biomechanics,* 34(7), p. 859-871.

196. Homminga, J., B.R. McCreadie, H. Weinans, and R. Huiskes (2003). The dependence of the elastic properties of osteoporotic cancellous bone on volume fraction and fabric. *Journal of Biomechanics,* 36(10), p. 1461-1467.

197. Bryant, J.D., et al. (1989). Rheology of bovine bone marrow. *Proc Inst Mech Eng H,* 203(2), p. 71-5.

198. Sandino, C., P. Kroliczek, D.D. McErlain, and S.K. Boyd (2014). Predicting the permeability of trabecular bone by micro-computed tomography and finite element modeling. *Journal of Biomechanics,* 47(12), p. 3129-3134.

199. Kohles, S.S. and J.B. Roberts (2002). Linear poroelastic cancellous bone anisotropy: trabecular solid elastic and fluid transport properties. *J Biomech Eng,* 124(5), p. 521-6.

200. Cardoso, L., et al. (2003). In vitro acoustic waves propagation in human and bovine cancellous bone. *J Bone Miner Res,* 18(10), p. 1803-12.

201. Prot, M., et al. (2012). Links between microstructural properties of cancellous bone and its mechanical response to different strain rates. *Comput Methods Biomech Biomed Engin,* 15 Suppl 1, p. 291-2.

202. Birmingham, E., et al. (2015). Mechanical stimulation of bone marrow in situ induces bone formation in trabecular explants. *Ann Biomed Eng,* 43(4), p. 1036-50.

203. Liu, X.S., et al. (2008). Complete volumetric decomposition of individual trabecular plates and rods and its morphological correlations with anisotropic elastic moduli in human trabecular bone. *J Bone Miner Res,* 23(2), p. 223-35.

204. Fields, A.J., et al. (2011). Influence of vertical trabeculae on the compressive strength of the human vertebra. *J Bone Miner Res,* 26(2), p. 263-9.

205. Hudelmaier, M., et al. (2005). Gender differences in trabecular bone architecture of the distal radius assessed with magnetic resonance imaging and implications for mechanical competence. *Osteoporosis International,* 16(9), p. 1124-1133.

206. Liu, X.S., et al. (2009). Micromechanical analyses of vertebral trabecular bone based on individual trabeculae segmentation of plates and rods. *Journal of Biomechanics,* 42(3), p. 249-256.

207. Shim, V.P.W., L.M. Yang, J.F. Liu, and V.S. Lee (2005). Characterisation of the dynamic compressive mechanical properties of cancellous bone from the human cervical spine. *International Journal of Impact Engineering,* 32(1–4), p. 525-540.

208. Vossenberg, P., et al. (2009). Darcian permeability constant as indicator for shear stresses in regular scaffold systems for tissue engineering. *Biomechanics and Modeling in Mechanobiology,* 8(6), p. 499.

209. Heneghan, P. and P.E. Riches (2008). Determination of the strain-dependent hydraulic permeability of the compressed bovine nucleus pulposus. *Journal of Biomechanics,* 41(4), p. 903-906.

210. Teo, J.C.M. and S.H. Teoh (2012). Permeability study of vertebral cancellous bone using micro-computational fluid dynamics. *Computer Methods in Biomechanics and Biomedical Engineering,* 15(4), p. 417-423.

211. Truscello, S., et al. (2012). Prediction of permeability of regular scaffolds for skeletal tissue engineering: A combined computational and experimental study. *Acta Biomaterialia,* 8(4), p. 1648-1658.

212. Yang, J., et al. (2002). Fabrication and surface modification of macroporous poly(L-lactic acid) and poly(L-lactic-co-glycolic acid) (70/30) cell scaffolds for human skin fibroblast cell culture. *J Biomed Mater Res,* 62(3), p. 438-46.

213. Jones, J.R. and L.L. Hench (2004). Factors affecting the structure and properties of bioactive foam scaffolds for tissue engineering. *J Biomed Mater Res B Appl Biomater,* 68(1), p. 36-44.

214. Boschetti, F., M.T. Raimondi, F. Migliavacca, and G. Dubini (2006). Prediction of the micro-fluid dynamic environment imposed to three-dimensional engineered cell systems in bioreactors. *Journal of Biomechanics,* 39(3), p. 418-425.

215. Md Saad, A.P., et al. (2017). The influence of flow rates on the dynamic degradation behaviour of porous magnesium under a simulated environment of human cancellous bone. *Materials & Design,* 122, p. 268-279.

216. Dias, M.R., P.R. Fernandes, J.M. Guedes, and S.J. Hollister (2012). Permeability analysis of scaffolds for bone tissue engineering. *Journal of Biomechanics,* 45(6), p. 938-944.

217. Jeong, C.G., H. Zhang, and S.J. Hollister (2011). Three-dimensional poly(1,8-octanediol–co-citrate) scaffold pore shape and permeability effects on sub-cutaneous in vivo chondrogenesis using primary chondrocytes. *Acta Biomaterialia,* 7(2), p. 505-514.

218. Mitsak, A.G., J.M. Kemppainen, M.T. Harris, and S.J. Hollister (2011). Effect of polycaprolactone scaffold permeability on bone regeneration in vivo. *Tissue Eng Part A,* 17(13-14), p. 1831-9.

219. Goldstein, A.S., et al. (1999). Effect of osteoblastic culture conditions on the structure of poly(DL-lactic-co-glycolic acid) foam scaffolds. *Tissue Eng,* 5(5), p. 421-34.

220. Böhm, H. (2004). *A Short Introduction to Continuum Micromechanics*, in H. Böhm, Editor. *Mechanics of Microstructured Materials*.(p. 1-40). Springer Vienna.

221. Liu, X.S., X.H. Zhang, and X.E. Guo (2009). Contributions of trabecular rods of various orientations in determining the elastic properties of human vertebral trabecular bone. *Bone,* 45(2), p. 158-163.

222. Yeatts, A.B. and J.P. Fisher (2011). Bone tissue engineering bioreactors: dynamic culture and the influence of shear stress. *Bone,* 48(2), p. 171-81.

223. Shi, X., et al. (2010). Type and orientation of yielded trabeculae during overloading of trabecular bone along orthogonal directions. *J Biomech,* 43(13), p. 2460-6.

224. Fyhrie, D.P. and M.B. Schaffler (1994). Failure mechanisms in human vertebral cancellous bone. *Bone,* 15(1), p. 105-109.

225. Stauber, M. and R. Müller (2006). Volumetric spatial decomposition of trabecular bone into rods and plates—A new method for local bone morphometry. *Bone,* 38(4), p. 475-484.

226. Castillo, A.B. and C.R. Jacobs (2010). Mesenchymal Stem Cell Mechanobiology. *Current Osteoporosis Reports,* 8(2), p. 98-104.

227. Kreke, M.R., L.A. Sharp, Y.W. Lee, and A.S. Goldstein (2008). Effect of intermittent shear stress on mechanotransductive signaling and osteoblastic differentiation of bone marrow stromal cells. *Tissue Eng Part A,* 14(4), p. 529-37.

228. Nauman, E.A., et al. (2001). Osteoblasts respond to pulsatile fluid flow with short-term increases in PGE(2) but no change in mineralization. *J Appl Physiol (1985),* 90(5), p. 1849-54.

229. McKercher, C.M., et al. (2009). Physical activity and depression in young adults. *Am J Prev Med,* 36(2), p. 161-4.

230. Krumm, E.M., O.L. Dessieux, P. Andrews, and D.L. Thompson (2006). The relationship between daily steps and body composition in postmenopausal women. *J Womens Health (Larchmt),* 15(2), p. 202-10.

231. Welch, R.D., C.E. Johnston, 2nd, M.J. Waldron, and B. Poteet (1993). Bone changes associated with intraosseous hypertension in the caprine tibia. *J Bone Joint Surg Am,* 75(1), p. 53-60.

232. Hu, M., J. Cheng, and Y.X. Qin (2012). Dynamic hydraulic flow stimulation on mitigation of trabecular bone loss in a rat functional disuse model. *Bone,* 51(4), p. 819-25.

233. Goulet, R.W., et al. (1994). The relationship between the structural and orthogonal compressive properties of trabecular bone. *Journal of Biomechanics,* 27(4), p. 375-389.

234. Hildebrand, T. and P. Ruegsegger (1997). Quantification of Bone Microarchitecture with the Structure Model Index. *Comput Methods Biomech Biomed Engin,* 1(1), p. 15-23.

235. Wang, J., et al. (2015). Trabecular plates and rods determine elastic modulus and yield strength of human trabecular bone. *Bone,* 72, p. 71-80.

236. Wang, J., et al. (2013). Trabecular Plate Loss and Deteriorating Elastic Modulus of Femoral Trabecular Bone in Intertrochanteric Hip Fractures. *Bone Research,* 1(4), p. 346-354.

237. Stein, E.M., et al. (2014). Skeletal structure in postmenopausal women with osteopenia and fractures is characterized by abnormal trabecular plates and cortical thinning. *J Bone Miner Res,* 29(5), p. 1101-9.

238. Kafka, V. (1983). A structural mathematical model for the viscoelastic anisotropic behavior of trabecular bone. *Biorheology,* 20(6), p. 789-93.

239. Bryant, J.D. (1995). Letter to the Editor: On hydraulic strengthening of bones. *Journal of Biomechanics,* 28(3), p. 353-354.

240. Anderson, J.J. (2000). The important role of physical activity in skeletal development: how exercise may counter low calcium intake. *The American Journal of Clinical Nutrition,* 71(6), p. 1384-1386.

241. Hwa, H.J. (2004). Could the intraosseous fluid in cancellous bone bear external load significantly within the elastic range? *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine,* 218(6), p. 375-379.

242. Stölken, J.S. and J.H. Kinney (2003). On the importance of geometric nonlinearity in finite-element simulations of trabecular bone failure. *Bone,* 33(4), p. 494-504.