PERIODICUM BIOLOGORUM
VOL. 117, No 1, 1–4, 2015

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Bone: biomechanic and endocrine function

VASILIJE NIKOLIĆ[1]
DRAŠKO PAVLOVIĆ[2]

[1] Retired professor of anatomy, Faculty of Medicine, University of Zagreb

[2] Department of Nephrology and Dialysis, Sestre Milosrdnice University Hospital, Zagreb, Croatia

Correspondence:
Prof.dr.sc. Vasilije Nikolić
Palmotićeva 23, 10000 Zagreb
E mail: vnikolic@mefos.hr

Received February 15, 2015.

Bones are part of the skeleton. They are distinguished by their density, hardness, and strength and are able to resist different mechanical forces, loads and stresses, such as compression, tension, bending, shearing or torsion. The primary functions of bones are mechanical support of the organism in resisting gravitational forces, enabling locomotion, mineral homeostasis, hematopoiesis, and the protection of internal organs. Bones can also be considered an endocrine organ.

The biomechanics of bone and bones is a science that uses the laws and methods of theoretical and applied technical physics and mechanics to solve biological and medical problems, researching mechanical characteristics of the biological organisms, systems, organs, or tissues and kinematics or kinetics, and moving of whole organism applying statics – a science of equilibrium of forces, and kinetics and kinematics, sciences of body movement. We can conclude that biomechanics is a multidisciplinary, interdisciplinary synthetic and multi-level science.

Bones were the most well-known morphological parts of the organism throughout the prehistory and history of the humanity. After putrefaction and decomposition of soft tissues, bones rested for thousands of years intact for macroscopic and microscopic investigation of morphology and strength. They are the only parts of organism believed to be without secrets. Through prehistory Man has known about animal and human skeletal morphology. Bones were even used as tools or weapons. Paleontology and anthropology could, through osteological tests, follow the evolution of many organisms, including human, and their physiology and pathology.

Life on the planet earth evolved inside the planet's gravitational field. This fact influenced ontogenesis and phylogenesis and the growth and the way of life of all living organisms. Today's current problems are investigations of living conditions with diminished or increased gravitational force in connection with space and other civil and military research programs.

Living organisms change through the time in almost all aspects: dimensions, volume, weight, structure, mass distribution, energy equilibrium, mobility of joints, and the mobility of the entire organism, or only its parts. Because of this fact, biomechanics is more complicated than its components: technical, biological or medical sciences. Biomechanics has overlapped many medical and clinical sciences (Figure 1), and also impinged on many other related professional branches (Figure 2). Now, when in scientific sphere, the decade, dedicated to investigation of bone and bones is finished, many secrets of bone now are well known, but not all. Living and dead bone materials are essentially different. How other supporting tissues, bone tissue consists bone cells and intercellular material. Osteoblasts, osteoclasts and osteocytes are cells enabling complicated bone metabolism, microscopic structure of bone, bone con-

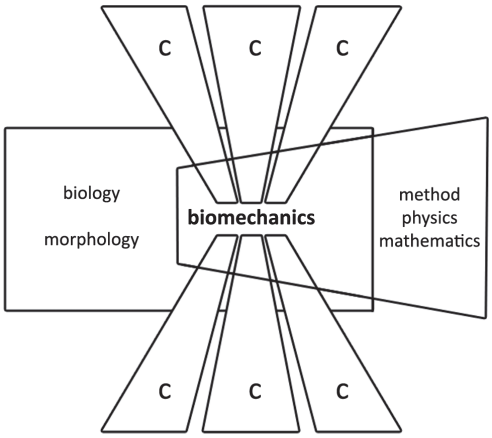

Figure 1. *Synthesis of biomechanics (C, clinic).*

struction, functional mechanical adaptation, electrical phenomena and aging effects. The family of bone cells include active osteoblasts, secreting intercellular organic matrix, inactive lining bone cells enveloping the endosteal surface of bone and the walls of the Harversian canals, osteocytes are converting from osteoblasts and are inserted in lacunae, multi-nuclear osteoclasts are differentiated from precursor cells and they dissolve and resorb bone *(1-7).*

Bone as Endocrine Organ

Bone has been traditionally viewed as a very dynamic organ. There is constant bone formation and bone resorption. Classically, bone function has been considered a mechanical one, i.e. the support and locomotion of the organism. Bone was also recognized as a target organ for several hormones, mainly parathyroid hormone, sex hormones and 1,25(OH)2 D vitamin *(8).* On the other hand, recent advances in the field of bone biology show that one type of bone cell, osteocytes, secrete a specific protein, sclerostin, which could act on other types of cells, osteoblasts, in paracrine fashion *(9).* Moreover, in the last few years, bone has been identified as a typical endocrine organ because of its capacity to secrete hormones in circulation. One hormone, osteocalcin, is involved in glucose and energy metabolism and another, fibroblast growth factor 23 (FGF 23), is involved in mineral homeostasis, or better to say phosphate metabolism *(10).* There also some other factors, e.g. sclerostin. It is a glycoprotein produced by osteocytes that inhibits bone formation *(11).* Bone morphogenetic proteins, besides bone formation properties, play a role in several clinical disorders, from, vascular calcification to obesity and diabetes *(12).*

Osteocalcin

Osteocalcin is a bone matrix protein produced by osteoblasts. Osteocalcin has 49 amino acids and is one of the most abundant non-collagen proteins in bone. The osteocalcin protein has three residues of the amino acid gamma-carboxyglutamine acid, on position 17, 21 and 24. Gama-carboxylation is vitamin K dependent and facilitates the binding of osteocalcin to hydroxyapatite in bone *(12, 13).* Vitamin D and parathyroid hormone are two major hormones involved in osteocalcin production – PTH through binding to the receptor PTH1R and vitamin D through a vitamin D responsive element located in the promoter region of BGLAP gene. There is no data that there are osteocalcin receptors. It seems that osteocalcin modulates the activities of the G-coupled (GPRC6A) protein receptor. A carboxylated form of osteocalcin is involved in the regulation of bone mineralization and is the modulator of bone cells, i.e. osteoblast and osteoclast activities *(14).* On the other hand, an uncarboxylated form of osteocalcin (unOC), is estimated to account for 50% of osteocalcin in the blood. Recent studies have demonstrated that the uncarboxylated form of osteocalcin is involved in energy and glucose metabolism *(15).* Experimental and clinical data represent unOC as a novel endocrine stimulator of insulin and adiponectin secretion. Recent studies report a positive feedback loop by which insulin via insulin receptors on bone cells, i.e. osteoblasts increase the decarboxylation of osteocalcin. The result is an increased blood level of unOC, which increases insulin sensitivity and insulin secretion *(16).* A few studies reported a positive correlation between higher blood osteocalcin level and lower fasting plasma

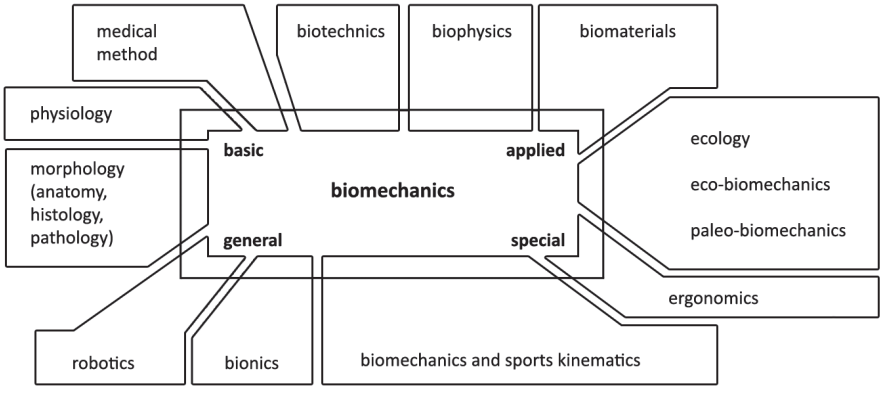

Figure 2. *Relationship between biomechanics and other scientific fields.*

glucose levels and better glycemic control *(17,18).* More experimental and clinical studies are need to confirm osteocalcin as an important factor in the reduction of insulin resistance, which, in turn, could prevent cardiovascular morbidity and mortality.

FGF 23

Fibroblast growth factor 23 (FGF 23) is a bone-derived hormone that regulates phosphate and vitamin D, 1, 25 hydroxyvitamin D metabolism. FGF 23 is a 251 amino acid protein, molecular weight 26 kDa. It was found to be synthesized and secreted by osteoblast, but recent studies have shown that osteocytes are more important in the synthesis and secretion of FGF 23 *(19).* At the beginning of this century, FGF 23 was recognized as a gene responsible for autosomal dominant hypoposphatemic rickets and a humoral factor responsible for tumor-induced osteomalacia. Today, the effect of FGF 23 on phosphate and vitamin D metabolism is well known. FGF 23 binds to receptors, FGFR1 receptors in the parathyroid cells and in distal convoluted tubule in the kidney. A cofactor, α-klotho, is needed for FGF 23 to bind to receptors. FGF 23 increases urinary fraction excretion of phosphorus by reducing the expression of sodium phosphorus cotransporter type II (NaPI II) and by suppressing 1 α-hydroxylase activity *(20).* Moreover, FGF 23 also enhances 24-hydroxylase activity, the effect of which is a decreased vitamin D level. Although the effect of FGF 23 on target organs, the kidneys (increased excretion of phosphorus, reduced synthesis and degradation of vitamin D) and parathyroid glands (reduced synthesis of parathyroid hormone), is well known, the regulatory mechanism of FGF 23 production is not sufficiently clear *(10).* There is no doubt that the phosphate level has some effect. Of interest are the findings that a high phosphate diet increases FGF 23 levels, but acute changes of serum phosphate do not alter it *(19).* Vitamin D increases the level of FGF 23. In addition to the effect on phosphate, vitamin D and PTH levels, there are reports indicating the role of FGF 23 level on blood vessel and heart. High FGF 23 levels are associated with the progression of left ventricular hypertrophy and aortic calcification, i.e. increased cardiovascular morbidity and mortality. This effect is probably indirect because there are no α-klotho coreceptors in blood vessels and the heart *(20, 21, 22).*

There is no doubt that osteocalcin and FGF 23 are hormones secreted by bone cells. In addition to its other important functions, bone is also an important endocrine organ.

Bone material is able to grow together with the organism by constantly rebuilding and remodeling its structure. From a rheological point of view bone material flows through the bones and skeleton. Skeletal diseases, such as osteoporosis, are usually manifested by mechanical failure, or bone fracture, most often as Colles' or hip fractures.

Experimental studies of the mechanical properties of bone are practically important in traumatological and orthopedic practice, particularly in investigations of bone fracture mechanisms and fracture healing.

Knowledge of the mechanical properties can predict the amount of load that a bone can bear and the amount of energy bone can absorb before fracturing. Material properties of substituted material, such as osteosynthetic or aloplastic devices, must be compatible with those of bones.

The geometry of bone, especially bone cross-section, is also an important biomechanical parameter and the best measure of the functional capacity of the skeleton related to its ability to sustain loads. The correlation coefficients between cross-sectional moments of inertia measured in vivo by non-invasive methods and calculated one and in vitro tested bending strength on isolated long bones is about 0,90 *(23).* One of the many problems of bone biomechanics is the relationship of mechanics and the material and geometrical properties of bone and aloplastic materials, such as osteosynthetic or prosthetic materials.

REFERENCES

1. ANTOLJAK T, HANČEVIĆ J, ŽAGAR Z, HAIMAN M, NIKOLIĆ V, HUDEC M, DAVILA S, BARILA ANTOLJAK N 1993 Influence of bone properties in originating proximal humeral fractures. *Period biol 95:* 213-216
2. BILIĆ R, KOLUNDŽIĆ R 2002 Computer in preoperative planing in orthopaedic surgery. *Period biol 104:* 269-275
3. HUISKES R, CHAO E Y S 1983 A survey of finite element analysis in orthopedic biomechanics. The first decade. *J Biomechanics 16:* 385-409
4. NIKOLIĆ V, HUDEC M 1988 Principi i elementi biomehanike. (Cro) Školska knjiga, Zagreb.
5. NIKOLIĆ V, PAVLOVIĆ D, ŽAGAR Z, NIKOLIĆ T, HUDEC M, HANČEVIĆ J, HAIMAN M 1994 Structure and strength of the distal forearm: Experimental Colles' fractures and mathematical modelling by finite elements methods. *Proceedings 10th international symposium on biomedical ingineering 95:* 62-64
6. NIKOLIĆ V, HUDEC M 2002 Past, present and future of biomechanics in Croatia. *Period biol 104:* 253-268
7. NIKOLIĆ V, HUDEC M 2011 Principi biomehanike (Cro), *Naklada Ljevak* Zagreb.
8. GUNTAR A R, ROSEN C 2012 Bone as an endocrine organ. *Endocr Pract 18:* 758-762
9. NEVE A, CORRADI A, CANTATORE F P 2013 Osteocalcin: skeletal and extra-skeletal effects. *J Cell Physiol 228:* 1149-53
10. VERVLOET M G, MASSY Z A, BRANDENBURG V M *et al.* 2014 Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders *Lancet Diab Endocrinol 2:* 427-436
11. CEJKA D, HERBERTH J, BRANSCUM A J *et al.* 2011 Sclerostin and Dickkopf-1 in renal osteodystrophy. *Clin J Am Soc Nephrol 6:* 877-82
12. YEAP BU B 2011 Osteocalcin:an endocrine link between bone and glucose metabolism *Expert Rev Endocrinol Metab 6:* 177-185
13. RAZZAQUE M S 2011 Osteocalcin: a pivotal mediator or an innocent bystander in energy metabolism? *Nephrol Dial Transplant 26:* 42-45

14. DiGIROLAMO D J, CLEMENS TH L, KOUSTENI S 2012 The skeleton as an endocrine organ. *Nat Rev Rheumatol 8:* 674-683
15. RIDDLE R C, CLEMENS T H L 2014 Insulin, osteoblasts, and energy metabolism: why bone counts calories. *J Clin Invest 124:* 1465-1467
16. CLEMENS TH L, KARSENTY G 2011 The osteoblast; an insulin target cell controlling glucose homeostasis. *J Bone Min Res 26:* 677-680
17. BOOTH S L, CENTI A, SMITH S R, GUNDBERG C 2013 The role of osteocalcin in human glucose metabolism: marker or mediator? *Nat Rev Endocrinol 9:* 43-55
18. VELDHUIS-VLUG A G, FLIES E, BISSCHOP P H 2013 Bone as regulator of glucose metabolism. *J Netherl Med 71:* 396-400
19. FUKUMOTO S FGF 23: phosphaten metabolism and beyond. 2010 *IBMS BoneKEy* 7: 268-278
20. NITTA K, NAGANO N, TSUCHIYA K 2014 Fibroblast growth factor 237klotho axis in chroic kidney disease. *Nephron Clin Pract 128:* 1-10
21. GUTIERREZ O M, MANNSTADT M, ISAKOVA T *et al.* 2008 Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med 359:* 584-92
22. ISAKOVA T, XIE H, YANG W *et al.* 2011 Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA 305(23):* 2432-9
23. MARTIN R B, BURR D B 1989 Structure, function and adaptation of compact bone. Raven Press, New York.