Medical Engineering and Physics 37 (2015) 719–728

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

From mechanical stimulus to bone formation: A review

Natacha Rosa [a,*], Ricardo Simoes [b,c], Fernão D. Magalhães [d], Antonio Torres Marques [a]

[a] DEMec, Faculty of Engineering, University of Porto, Rua Roberto Frias, 4200-465 Porto, Portugal
[b] Polytechnic Institute of Cávado and Ave, School of Technology, Campus do IPCA, 4750-810 Barcelos, Portugal
[c] Institute for Polymers and Composites IPC/I3N, University of Minho, Campus de Azurem, 4800-058 Guimarães, Portugal
[d] LEPABE - Faculdade de Engenharia, Universidade do Porto, Rua Roberto Frias, 4200-465 Porto, Portugal

ARTICLE INFO

Article history:
Received 16 August 2014
Revised 12 May 2015
Accepted 31 May 2015

Keywords:
Bone
Muscles
Mechanical stimulus
Mechanotransduction
Test model
Osteocyte

ABSTRACT

Bone is a remarkable tissue that can respond to external stimuli. The importance of mechanical forces on the mass and structural development of bone has long been accepted. This adaptation behaviour is very complex and involves multidisciplinary concepts, and significant progress has recently been made in understanding this process. In this review, we describe the state of the art studies in this area and highlight current insights while simultaneously clarifying some basic yet essential topics related to the origin of mechanical stimulus in bone, the biomechanisms associated with mechanotransduction, the nature of physiological bone stimuli and the test systems most commonly used to study the mechanical stimulation of bone.

1. Introduction

Understanding the influence of mechanical stimuli on the structure of bone has long been a topic of scientific interest. To the best of our knowledge, Galilei [1], noticed a relationship between body weight and bone size and shape. However, mechanical forces were not identified as responsible for shaping the architecture of the skeleton until the 19th century, in studies developed by Meyer [2], Culmann [3] and Roux [4].

The German anatomist von Meyer identified arched trabecular patterns in a sagittally sectioned human first metatarsal and calcaneus, and Culmann, a pioneer of graphical methods in engineering, suggested that the patterns appeared to be aligned along principal stress directions produced by functional loading [5]. In 1881, Roux proposed that the apposition and absorption of bone is a biological stress-controlled process [6,7].

However, Julius Wolff [8] – influenced by von Meyer–Culmann interactions in 1867 – became associated to the concept of bone adaptation. He claimed that the shape of bone is related to mechanical stress by *Wolff's law of bone transformation*. Although this law is an overly simplified mathematical approach, the concept has been accepted by the scientific community. Recent interpretations of "Wolff's Law" have proposed that bone mass and architecture are to some extent governed by adaptive mechanisms that are sensitive to their mechanical environment [9–11].

Over the years, remarkable work has been done to elucidate bone mechanotransduction and its response to mechanical stimulation. The first contact with this subject can be overwhelming due to the complexity and multidisciplinary mechanisms involved. This review paper aims to establish the state of the art of this area while simultaneously clarifying some basic yet important questions on which light has been shed during recent years, such as

- What is the origin of the mechanical stimulus? How is it triggered?
- How does bones mechanotransduction work?
- What are the normal physiological bone stimuli?
- What test systems are commonly used to study bone's mechanical stimulation?

2. Mechanical stimulus

Bone mass is maintained by and adapted to mechanical strain, primarily as the result of muscular contraction [12,13]. Some key aspects are currently accepted by the scientific community at large and should be mentioned.

First, long bones deformation is obtained by an orchestrated muscle activity as demonstrated by Duda et al. [14]. Using a finite element strain distributions model, these authors concluded that simplified load regimes produced differences in strain as high as 26% compared with regiments that included all thigh muscles. Although this study

* Corresponding author. Tel.: +351 912 998 562.
E-mail address: natacharosa22@gmail.com (N. Rosa).

http://dx.doi.org/10.1016/j.medengphy.2015.05.015
1350-4533/

focused only on the proximal femur situation, this concept can be generalized to other bones in the human body.

Second, the forces experienced by bone arise from muscle action rather than from mere gravitational forces [15]. Hence, muscle mass/strength correlates with bone strength [12]. This concept was demonstrated in a study by Sievänen et al. [16]. The patella bone mineral apparent density and average strain magnitude were measured in a chained event experiment that included one-year unilateral strength training interventions, an accidental knee ligament rupture and a two-year rehabilitation period. The patella was selected as the target bone because it is a non-weight-bearing bone that receives mechanical stimuli from only the quadriceps activity. Sievänen et al. showed that a decline in muscle mass precedes a decline in bone strength under conditions of disuse and that the recovery of muscle mass increases before bone mass. In another study, Schönau et al. [17] compared the muscle development with age as well as muscle development and bone strength.

Disuse can be asserted to cause muscle wasting and bone loss, whereas physical activity increases muscle strength and bone mass. However, according to Rittweger et al. [15], this relationship only holds to a certain extent. The authors claim that muscular exercise can only enhance bone strength up to 1–2% because tendon stiffness may limit the musculoskeletal peak forces.

In several studies [9,12,16,18], a time lag of up to 5 days was registered between a single period of mechanical loading *in vivo* and the onset of collagen and mineral apposition increases on the bone surface. This phenomenon is justified by the delay between the initial formation of new bone and the establishment of fully mineralized and mature bone.

The third key aspect was stated in one of the earliest far-reaching interpretations of bone loading made by Pauwels [19], who suggested that bending moments are transmitted along limbs by a combination of tensile forces in the muscle and compressive forces on bone. Hence, gravitational forces tend to lower and collapse our body segments in any upright posture. However, bending moments are accentuated rather than reduced due to the physiological curvature of long bones. In response to these external loads, muscles not only provide the necessary moment equilibrium in joints, but they counteract the passive bending moments along bones in an energetically efficient manner, as stated by Munih et al. [20]. While reducing the bending stress, muscles increase the axial compressive load irrespective of the posture to ensure minimal bone stress and minimal bone weight [21]. From all registered loading modes in long bone, bending is the most significant for bone adaptation [22–24].

Fourth and last, in addition to mechanical stimuli, bone remodelling may also be regulated by hormones, such as estrogen and parathyroid hormone [25,26], and induced by the nervous system [18,27] and inflammatory reactions [28].

3. Mechanotransduction system

Over the last several years, osteocytes have become generally accepted as the mechanosensory cells within the bone. Osteocytes coordinate the remodelling process by converting external mechanical forces into biochemical responses – a process known as mechanotransduction. However, the mechanism by which these cells sense the mechanical loads and facilitate adaptive alterations in bone mass and architecture is not yet completely understood [10,18,29,30].

3.1. Stimuli perceived by osteocytes

Osteocytes are generally assumed to react to bone deformation or to one of the consequences of bone deformation, such as shear stress due to load-induced fluid flow, electric fields caused by stress-generated streaming potentials, and hydrostatic pressure [22,31,32].

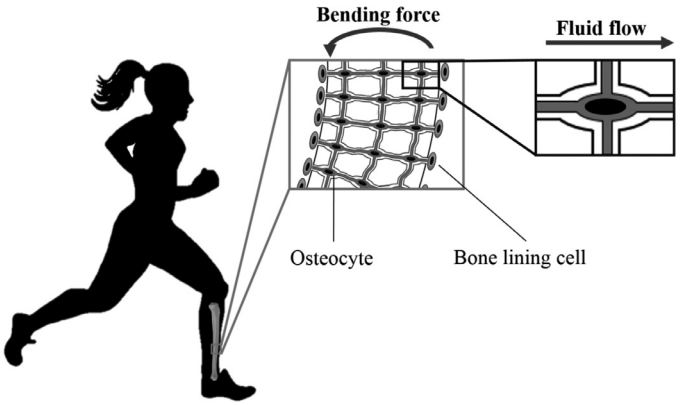

Fig. 1. Schematic representation of mechanical loading that causes interstitial fluid flow through bone's lacuna-canalicular network (adapted from Duncan et al. [9]). The tension/compression stresses associated with bending cause a pressure gradient that promotes fluid flow along the osteocytes.

3.1.1. Cell deformation

The immediate consequence of mechanical loading is strain, which is a small deformation throughout the calcified matrix. These stimuli will stretch the osteocytes to the same extent as the surrounding bone tissue. When stretched in one direction, bone tends to slightly contract in the perpendicular direction. Hence, direct biaxial osteocyte strain is common [9,33]. Several authors [33–35] suggest that the strains experienced by an osteocyte are much higher than those measured on the bone surface, with registered amplification factors that are up to 9 times larger than the applied global strain. This difference may be due to a magnification effect caused by the cell's complex surrounding pericellular and extracellular matrix. In a recent study, Wang et al. [36] proposed that the strain amplification factor positively correlates with the loading frequency and loading strain.

3.1.2. Shear induced by fluid-flow

Loading the bone first pressurizes the interstitial fluid around the osteocytes before flow is initiated [32]. A study developed by Gardinier et al. [37] predicted that *in vivo* osteocytes could experience hydrostatic pressures of up to 5 MPa. The interstitial fluid within the lacuno-canalicular (LC) is then driven to flow through the thin layer of non-mineralized pericellular matrix surrounding the osteocytes and towards the Harversian or Volkmann's channels [22,32]. In this sense, bone can be compared to a water-soaked sponge. A compressive force on the sponge will squeeze water out of it. Similarly, mechanical loading will result in a flow of interstitial fluid through the LC network of bone (see Fig. 1) [38]. The flow of interstitial fluid through the LC network places shear stress on the cell membranes. This stress is thought to initiate a biochemical response from the cells [39].

Piekarski [40] was the first researcher to propose that mechanical loading induces fluid-flow in bone. He stated that this flow enabled nutrition and waste removal.

The effect of the three-dimensional LC network complex geometry of bone on the fluid flow shear stress stimuli mechanism and its role in osteocyte mechanobiology are not yet fully understood. However, a recent study developed by Verbruggen et al. [41] showed that individual osteocytes may be subjected to a maximum shear stress stimulus of approximately 11 Pa and an average fluid velocity of 60.5 μm/s in response to vigorous activity. Mechanosensing bone cells also seem to be able to sense low fluid-flow stress values, as demonstrated by Morris et al. [42], Delaine-Smith et al. [43], Young et al. [44].

Several studies have also evaluated the responsiveness of bone cells to different flow profiles. Of these studies, we would like to highlight the important work developed by Jacobs' group [45–47], in