Effect of changes in microstructure on the growth of blood vessels and the development of osteophytes during osteoarthritis

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Abstract

Proposed novel mathematical formulation considers influence of microdamage on the angiogenesis and osteophyte development during osteoarthritis (OA). The causes of OA - mechanical overloadings, focused stresses - generate microdamages in the subchondral layer and can induce chondrocytes apoptosis. Both of these phenomena are a contributor to the beginning of angiogenesis and bone remodelling. New osteophytes - bone spurs grow into the cartilage tissue bringing the pain on the daily movements.

Keywords: osteoarthritis, mathematical modelling, angiogenesis, osteophyte, mechanical loading

1. Introduction

Osteoarthritis (OA), also known as degenerative joint disease, is the most common type of joint disease. Osteoarthritic joints become stiffer and the movements start to be painful. Now it is known that OA is a disease of the bone as well as the cartilage although the phenomenon is still not fully understood. Due to the social aspects of the disease, all attempts to identify and improve predictions are noteworthy. The model presented here may contribute to wider understanding of the OA and help to bring some factors to inhibit joint degeneration.

2. Concepts and assumptions

Bones are very rigid and vascularized compared to the articular cartilage, which is flexible with no vascular network. Due to bones supporting structure and the slick surface and shock absorption properties of cartilage, smooth motion is possible. When the osteoarthritis occurs, the mechanical properties degenerate, regretfully. The main cause of degenerative joint disease are mechanical loads which violate biological equilibrium [1]. Overloaded, hypertrophied cells dying and produce biochemical factors to obtain more nutrients in the form of vascular endothelial growth factor (VEGF). It is one of main stimuli for angiogenesis - process of developing new blood vessels [2]. On the other hand, for a various reasons, focused stresses can appear during daily work. These can lead to the concentrated changes - microcracks in the subchondral region or even in the cartilage of the joint. To regenerate the damaged regions, the process of bone remodelling begins [3], whereby blood vessels start to grow in the specific direction. Consequently, osteophytes - bone spurs - are developed during OA abundantly and movement becomes stiff and painful, subchondral layer gets thicker and cartilage layer gets thinner.

In order to propose an acceptable mathematical model some essential assumptions had to be defined: (i) there is a composite of bone and cartilage, whose porosity depends on contribution of the cartilage in the composite. The more cartilage the bigger porosity (ii) signals decrease exponentially with distance from the source (iii) mechanical overloading signal S_{MC} for angiogenesis is represented by a difference between the actual elastic strain energy density and mechanical loading safety limit acceptable for a cell (iv) biological undernutrition signal S_B is proportional to the considered in numerical difference between nutrients demand and actual volume of examinations nutrients (v) mechanical stimulus S_{ME} for Young modulus changes is proportional to the difference between the actual elastic strain energy density and the reference value of energy associated with biological equilibrium (vi) at the beginning of the process blood vessels and bone cells are present only in the bone domain (vii) at the beginning of considered process Young modulus of bone is much greater than Young modulus of cartilage (viii) due to some non-physiological changes in posture or joint the concentrated force is applied to the composite [4] (ix) rate of microdamage depends on deformation and rate of bone remodelling.

3. Formulation of system of integro-differential equations

The presented system of non-linear integro-differential equations is associated with non-local effects.

Evolution of blood vessels density $\rho_V(\mathbf{x},t)$

$$\frac{\partial \rho_V(\mathbf{x},t)}{\partial t} = \kappa B_1(\underbrace{A_1 C_2}_{I} + \underbrace{A_2 C_1}_{II}) \tag{1}$$

First formula Eq.(1) associated with development of blood vessels' density consists of two parts: biological (I) and mechanical (II) effects, where

$$C_1 = \int\limits_{\Omega} S_B(\boldsymbol{\zeta},t) e^{-\frac{R}{\beta}} d\zeta_1 d\zeta_2 d\zeta_3,$$

$$C_2 = \int\limits_{\Omega} P_C(\boldsymbol{x},t) S_{MC}(\boldsymbol{\zeta},t) e^{-\frac{R}{\xi}} d\zeta_1 d\zeta_2 d\zeta_3,$$

S_{MC} - the mechanical signal for blood vessels growth released by overloaded dying chondrocytes,
P_C - mikrostructure coefficient,
$\frac{R}{\gamma}, \frac{R}{\beta}, \frac{R}{\xi}$ - range of signals.

Both biological and mechanical phenomena associated with part (I) and (II) have significant effects only within a close proximity to existing vascular network. Consequently, the non-local effect of angiogenesis is included in factor B_1 used to 'scale' quantity of blood vessels density.,

$B_1 = A_8 \int\limits_{\Omega} \rho_V(\boldsymbol{\zeta}, t) e^{-\frac{R}{\gamma}} d\zeta_1 d\zeta_2 d\zeta_3$ - angiogenesis.

An implemented κ - microstructures changes influence the process of angiogenesis. Microdamage evolution was formulated following the bone remodelling algorithm proposed by Lekszycki et al. [5].

Next equation Eq.(2) relating to the excessive density of nutrients consists of two parts. First part (III) depends on standard formula for nutrients consumption and density of bone cells. The higher density of bone cells the lower density of nutrients. Second part (IV) informs that density of nutrients increases with supply from blood vessels.

Evolution of density of nutrients $\rho_N(\mathbf{x}, t)$

$$\frac{\partial \rho_N(\mathbf{x}, t)}{\partial t} = \underbrace{-A_5 \eta(\mathbf{x}, t) \rho_B(\mathbf{x}, t)}_{III} + \underbrace{A_6 B_2}_{IV} \tag{2}$$

where,
$B_2 = \int\limits_{\Omega} \rho_V(\boldsymbol{\zeta}, t) e^{-\frac{R}{\alpha}} d\zeta_1 d\zeta_2 d\zeta_3$ - angiogenesis,
$\eta(\mathbf{x}, t) = \frac{\eta_m \rho_N(\mathbf{x}, t)}{K_s + \rho_N(\mathbf{x}, t)}$ - formula defined by Monod [6],
ρ_B - density of bone cells,
$\frac{R}{\alpha}$ - range of signals.

Evolution of density of bone cells $\rho_B(\mathbf{x}, t)$

In the formula Eq.(3) we adapted the formula proposed by Verhulst [7] for density of cells in culture in order to describe density of bone cells. First part (V) controls increasing density of bone cells by supply of nutrients for cells which can proliferate only from the existing cells. It is assumed however, the bone cells density increases too much, the negative part of cells interactions (VI) predominates

$$\frac{\partial \rho_B(\mathbf{x}, t)}{\partial t} = \underbrace{\eta(\mathbf{x}, t) \rho_B(\mathbf{x}, t)}_{V} - \underbrace{A_3 \rho_B^2(\mathbf{x}, t)}_{VI} \quad . \tag{3}$$

The last equation Eq.(4) for changes of Young modulus depends on non-local mechanical effect and density of bone cells.

Equation of changes of Young's modulus $E(\mathbf{x}, t)$

$$\frac{\partial E(\mathbf{x}, t)}{\partial t} = b_r \rho_B(\mathbf{x}, t) \int\limits_{\Omega} S_{ME}(\boldsymbol{\zeta}, t) e^{-\frac{R}{\vartheta}} d\zeta_1 d\zeta_2 d\zeta_3 \tag{4}$$

where,
S_{ME} - the signal for Young's modulus changes refers to the difference between the actual elastic strain density and the reference value,
b_r - bone remodelling coefficient,
A_{1-i} - weight parameters.
The exponential term approximates decreasing density of nutrients at the distance R from the source
$R = \sqrt{(x_1 - \zeta_1)^2 (x_2 - \zeta_2)^2 (x_3 - \zeta_3)^2}$.
The integrals enable summation at the certain position x of the considered variable located at ζ.
Signals decrease exponentially with distance from the source.

4. Initial and boundary conditions

Bone and cartilage domains are perfectly connected to each other. At the beginning of the process blood vessels and bone cells are present only in the bone domain as well as bone Young modulus is much greater than Young modulus of cartilage. Due to some non-physiological changes in posture or joint in addition to the uniform pressure, the concentrated force is applied to the composite (Fig. 1a).

5. Results and conclusions

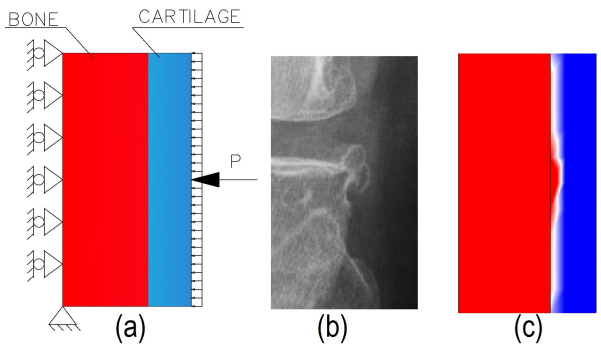

Figure 1: Schematic geometry considered in numerical calculations (a), x-ray image of osteophyte development in the knee joint (b), results of numerical calculations of changes of bone cells density (c).

Presented model of development of the osteophytes during OA includes angiogenesis process, mechanical loading and changes to tissue microstructure. The model takes into consideration non-local and non-linear mechano-biological effects. Due to the complex nature of the system of equations and the large number of parameters, the results are highly sensitive to small variations in the parameters and show possible numerical instability. Despite this, the results of numerical calculations (Fig. 1c) are associated with the clinical observations of development of osteophytes during osteoarthritis and reflect the complex nature of joints changes during osteoarthritis (Fig. 1b).

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