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Personalized Regenerative Rehabilitation of Osteoarthritis Based on Mechanical Loading and Mechanoregulation

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ABSTRACT

Osteoarthritis is one of the most important “civilizational diseases" that significantly restricts quality of life and active life expectancy. The current practice of treating patients with osteoarthritis often consists in replacing damaged natural joints with artificial ones. Even if the replacement procedure is successful, various complications may occur in the post operation period causing health problems in the long term. The purpose of the current research is to develop methods of regenerative rehabilitation of joints on the basis of personalized treatment technologies of osteoarthritis. This goal can be achieved through the development of programmed mechanical loading of joints taking into account modern knowledge about mechanoregulation of cells, as well as applications of tissue-engineered structures using induced pluripotent stem cells. Local regeneration processes can be supported by targeted delivery of microcapsules of multicomponent lubricants, as well as drugs.

1. Introduction

The subject of this paper are the natural joints of our body. Their function is to carry loads and to allow for free and controlled movement. But all moving parts, whether natural or artificial, are subject to wear. In the case of natural joints, the wear is compensated by tissue formation. Bone and joint remodeling maintain the metabolic homeostasis and structural integrity via precise coordination of bone resorption and bone formation. However, if for some reason – mechanical or metabolic – the wear and degeneration processes prevail, this can eventually lead to disfunctions of the joint – osteoarthritis (Figure 1), which is not at all a rare decease: For example, 16 percent of the world population suffer from knee osteoarthritis [1]. According to German statistics, diseases of the musculoskeletal system like osteoarthritis make up one of three approximately equally represented degenerative diseases affecting the quality of life, activity and working capability of people aged

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between 50 and 65 years, the other two being nutritional and metabolic diseases and diseases of the circulatory system [2].

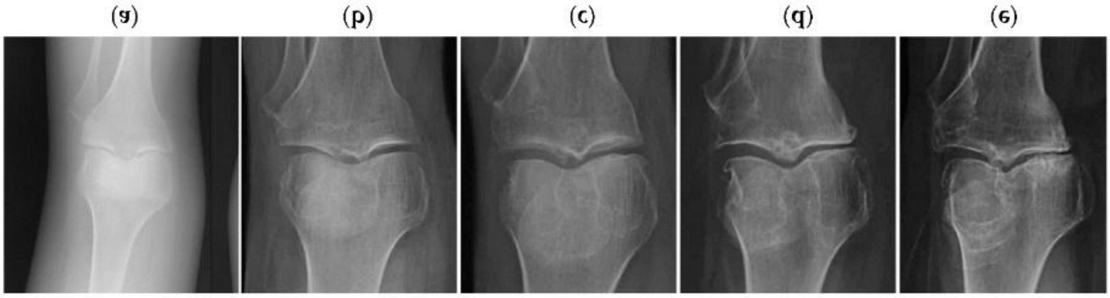

Fig. 1. Osteoarthritis of the knee joint [3]

Let us look at the hip joint. The hip joint is perhaps the most classic of all joints. From a mechanical point of view, it is an almost ideal ball-and-socket joint. The surfaces of the joint are covered by cartilage, and the space inside the joint capsule is filled with synovial fluid. Cartilage is a viscoelastic tissue that consists of 65 to 80% of water, which fills the collagen matrix. The entire tissue is kept alive by the cartilage cells - chondrocytes. The content of chondrocytes in cartilage is however very low, around 1-2% of the cartilage volume. Cartilage and synovial fluid have unique properties, especially an extremely small coefficient of friction of around 1/1000 [4].

2. Dual Role of Mechanical Loading for Articular Cartilage

Mechanical loading plays a dual role in cartilage. On the one hand, the load is necessary to maintain the normal functioning of the cartilage. Cartilage tissue does not contain blood vessels. The nutrition of cartilage cells is due to the diffusion of nutrients and oxygen from the synovial fluid located in the interarticular space. To activate these diffusion processes, periodic mechanical loading of the joint is necessary. In Figure 2, development of the pore pressure and the flow of synovial fluid in a cartilage layer under periodic normal loading is shown. We see the pumping effect, similar to that by heart. The cartilage was modeled as an elastic porous material filled with a viscous fluid. Normal loading leads to appearance of a pressure gradient in the porous matrix and fluid which causes a viscous flow through the matrix. In the absence of periodic loading, the supply of oxygen and nutrients ceases, which can lead to degeneration of cartilage.

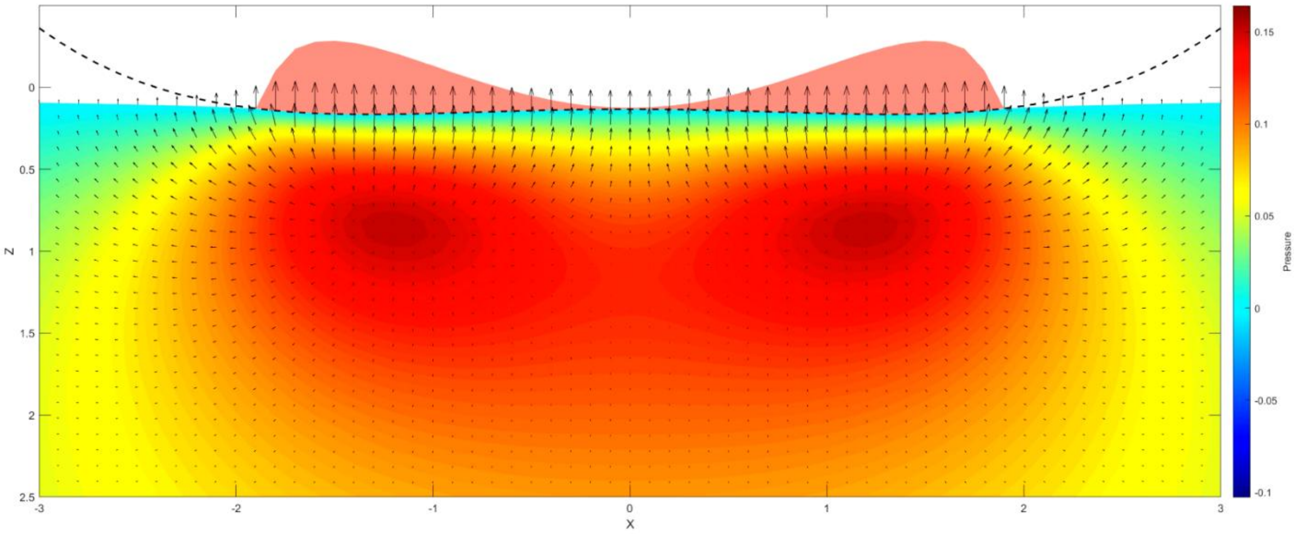

Fig. 2. Pressure distribution and flow in a cartilage layer subjected to a periodic normal load (a snapshot from a video produced using the method described in [5]

On the other hand, excessive mechanical loading can lead to wear and discontinuities in the cartilage body [6][7]. Therefore, the key question for maximizing cartilage health is therefore how to load the joint properly to promote the development of regenerative effects, while minimizing wear, in particular by difgferentiation of stem cells to cartilage cells and their growth. The behaviour of stem cells, including their differentiation into cartilage cells, can be influenced by mechanical loading and the biophysical properties of their cellular microenvironment [8].

From a mechanical point of view, the situation is very simple: The normal loading is a “good” and tangential loading is a “bad”. It is well known, for example from the Hertz contact theory, that a normal load leads to an increase in the diagonal components of the stress tensor, which means the increase in hydrostatic pressure. At the same time, shear stresses that have a negative effect on the joint remain quite small. The pressure gradient during normal loading has the “pump effect” and promotes the diffusion of extracellular fluid from the surface to deeper layers of cartilage (Figure 3a).

Tangential stresses, on the other hand, can be dangerous for the material of the joint, and they have no “pump effect” as they do not lead to dilatation (Figure 3b). In addition, tangential stresses at the trailing side of the contact cause the occurrence of tensile stresses in the material. The development of such stresses creates conditions for fracture of the cartilage tissue. Basically, we all know these properties from our everyday life. It is difficult to cut a loaf of bread by just pressing a knife on it, but relatively easy with a tangential cutting motion. In living systems, both of these effects are further amplified by the response of cells to mechanical stresses – normal and tangential – and the release of corresponding enzymes.

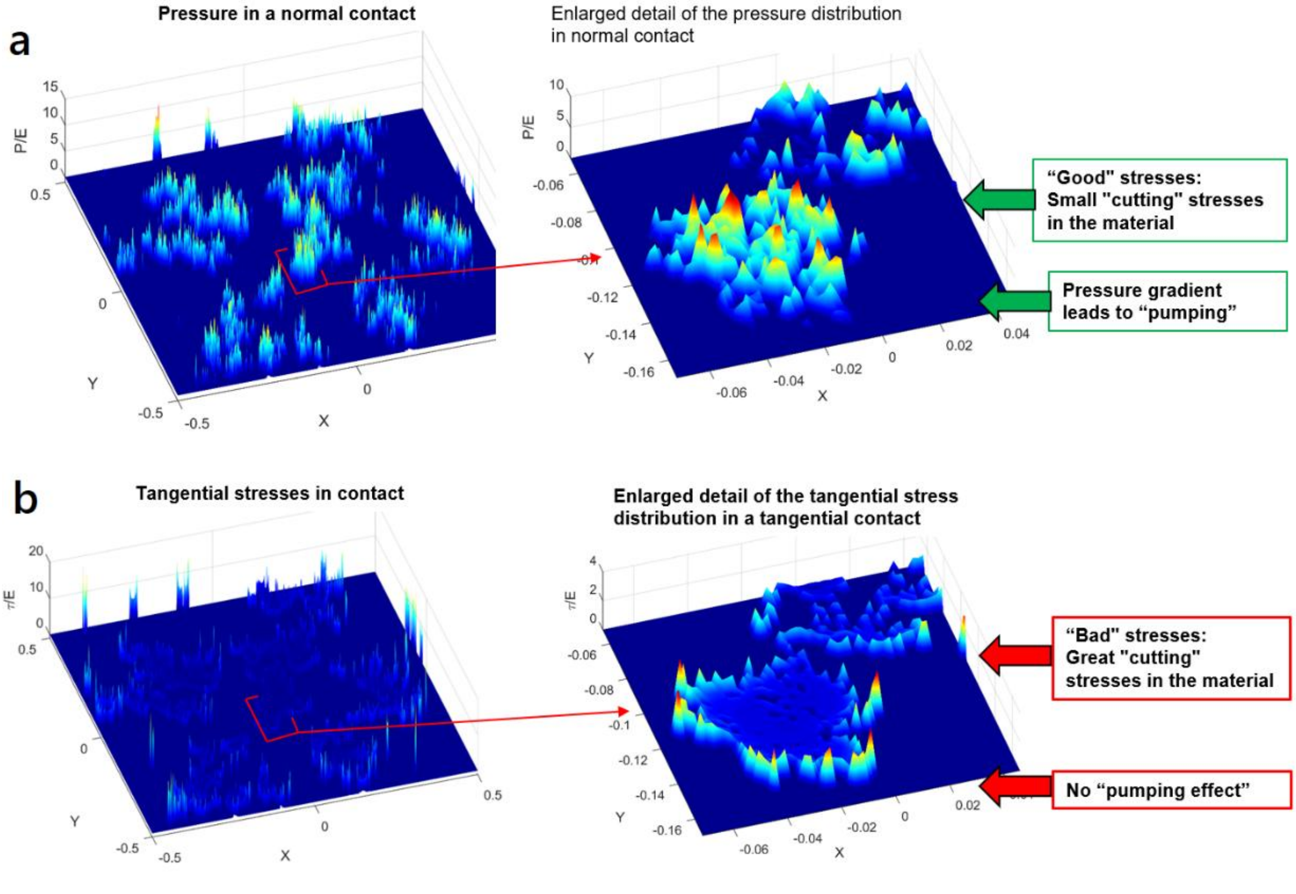

Fig. 3. (a) Normal loading in a contact produces a pumping effect due to gradient of pressure inside the medium (not shown in the Figures) while minimizing harmful tangential stresses; (b) tangential loading leads to high cutting stresses while having no pumping effect

3. Structural Analysis of Friction in Joints

Let us for a moment go back to the purely mechanical level and discuss friction in the joint. The friction force is determined by the friction coefficient and the pressure in the joint which is due to either gravitation or tension of muscles. The healthy function of the joint consists in the joint being loaded from time to time. But in between it must be completely relieved of load. It's just like walking - we transfer the load from one leg to the other. The body is supported continuously, but the movement takes place in the leg that is not currently being loaded. This is exactly how a joint should ideally be loaded.

One disease of civilization, however, is that we spend a lot of time in front of the computer or generally sitting in certain positions. We move little and use only a small range of all possible degrees of freedom of our body. Certain muscles get used to the shortened state. And when a person stands up, the opposing muscles have to be used. They do their job and bring the body into the right position. But this puts a tension on the joint from both sides, which leads to increased pressure. This means that even if the external load is removed from the joint, as when walking, it is still not completely relieved and has to slide under pressure. This means that the friction force is high, heat is generated, and wear increases. It is as if we would not transfer the load completely from one leg to the other when walking but tried to move forward by sliding our feet. This is possible, but it involves large losses of energy and material.

The countermeasures are well known. They consist, on the one hand of stretching the muscles and connective tissue through special stretching exercises and, on the other hand, of relaxing the muscles, e.g. through appropriate massages or meditation. These are all measures to reduce the minimal pressure force in joints. The ability of a joint to be completely unloaded is the basic prerequisite for its proper function and longevity, independently of whether it is a healthy natural joint or an artificial joint. For artificial joints, this is even more important.

4. Articular Cartilage Wear, Growth and Remodeling

Let us look in more detail at the cartilage structure. To 65-80% percent it consists of water and to 20 to 35 % of a porous extracellular matrix (ECM). Like all other tissues, hyaline cartilage develops from unspecialized stem cells. Under favorable external conditions, the stem cells differentiate into chondroblasts which quickly secrete the ECM. They are eventually surrounded by the extracellular matrix and separated from each other. Easy access to oxygen and nutrients is disrupted and is further ensured by diffusion through ECM to the cell. The metabolism of the cartilage cells decreases; then they are called chondrocytes.

All these processes are controlled by mechanical stresses [9] [10]. The chondrocytes are induced by mechanical stresses to perform such actions as proliferation, final differentiation, synthesis or catabolism of ECM. The dependence of the phenotypic response of chondrocytes on mechanical stimuli is called mechanotransduction or mechanoregulation. At the moment, the most promising approach for understanding mechanoregulation is using empirical data on the response of cells to mechanical load. Using a realistic mechanical model of cartilage as a porous fluid filled matrix, it is possible to solve the contact mechanical problem and find the flows and the stresses in the matrix and the fluid [11][12]. An experimental study on osteoarthritis-induced mice has shown that mechanical loading reduces endoplasmic reticulum stress and promotes autophagy, which improves cartilage structure and reduces the symptoms of osteoarthritis, which can be seen as a disease of the cartilage pericellular matrix [13][14]. Electromicroscopic analysis shows that osteoarthritis leads to degeneration of the rough endoplasmic reticulum, which can be suppressed by applying mechanical stress. Therefore, excessive endoplasmic reticulum stress in later stages of osteoarthritis can be suppressed by inducing mechanical stress [13]. A study of the effects of mechanical loading on human mesenchymal stem cells has been carried out to develop a tissue engineered cartilage for efficient articular cartilage repair [15]. The developed "Rigidity Percolation"- Model describes the mechanical interaction between collagen and aggrecan networks in cartilage, which determines the shear mechanics of cartilage. Experiments have shown that small changes in the concentration of collagen and aggrecan can weaken the shear modulus [16].

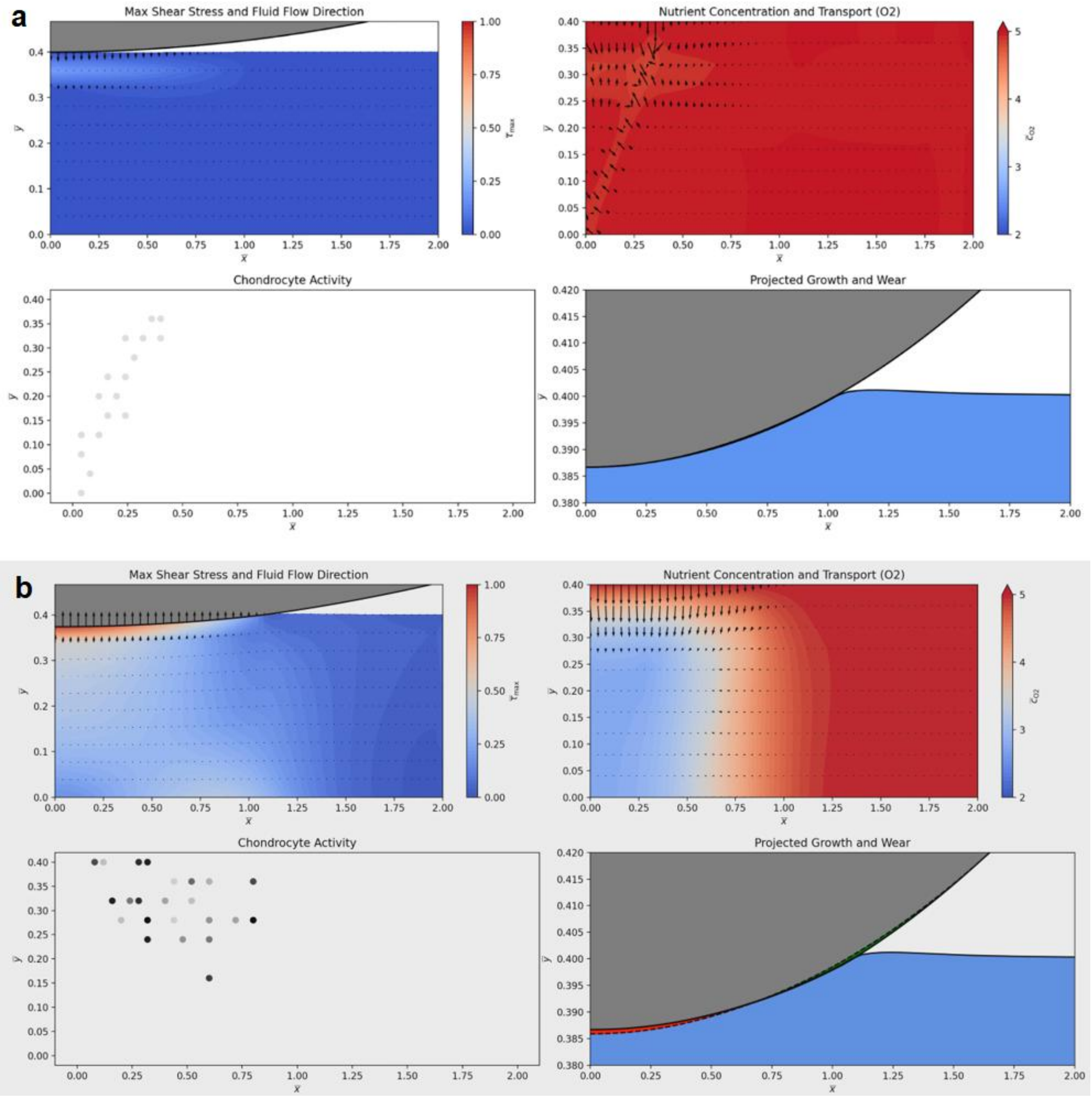

Fig. 4. Stress distribution, flow of the synovial fluid, activity of chondrocytes, and growth of cartilage. (a) and (b) are two snapshots from a simulation using the method described in [5]. The stress tensor determined in the model of fluid-saturated porous medium (respectively left upper subfigure). Based on the stressed state, the activity of chondrocytes has been determined (respectively bottom left figure). This activity lead to an oxygen depleted region (as shown be blue color on the upper right figure. Activity of chondrocytes lead to a cartilage growth shown in the bottom right sub-figures

The results of empirical studies of mechanoregulation should be used to determine how the cells proliferate, differentiate, generate the matrix, migrate, and finally die. This allows us to see how various loading scenarios influence health or the healing of the cartilage. Based on such simulations, one can vary the regimes of mechanical loading and optimize them for the optimal regeneration and the smallest wear and degeneration [13]. Figure 4 illustrates a simulation of all the above-mentioned factors.

5. Robotic Assistance and Surgery

For realizing the optimum loading scenarios, robotic assistance may be needed, which is especially important in the case of complicated loading scenarios. If there is a larger damage of cartilage or it is completely destroyed at some location, then natural regeneration is not possible. At present there are several techniques to support growth and regeneration by scaffolds. Basically, the defect area is covered by a degradable material containing chondrocytes. The following controlled loading leads to the proliferation of cells and production of the extracellular matrix followed by degeneration and disappearance of the scaffold material [17]. Autologous chondrocyte transplantation involving acquiring hyaline cartilage from a biopsy and then transplanting it to the injured site has shown the problem that in this procedure collagen I is secreted, which leads to formation of a fibrous tissue. A possible solution to this problem could be expanding not the chondrocytes but the induced pluripotent stem cells [18] [19]. All off the above procedures can be supported by the targeted delivery of drugs and bio-lubricants [20].

6. Conclusion

The existing knowledge on mechanoregulation can be used for developing predictive models of regenerative rehabilitation of joint tissues with the aim of creating personalized technologies of treatment of osteoarthritis of the joints. To achieve this goal, the following steps have to be done:

i. Development of methods of programmed mechanical action on joints taking into account modern knowledge of cell mechanotransduction.
ii. Creation of robotic complexes that allow the implementation of the required loading program.
iii. Development of tissue-engineered constructions using induced pluripotent stem cells.
iv. Development of methods for intensifying local regeneration processes by targeted delivery of multicomponent lubricants, as well as medicinal and stimulant agents, using microcapsules.

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Data Availability Statement

This study did not report any data.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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