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Pain in Osteoarthritic Joints: Biological Signaling and 3D Models based on Imaging

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs Universitet kommer att offentligen försvaras i R-aulan, Sahlgrenska Universitetssjukhuset, Mölndal, fredagen den 24 januari 2020, klockan 09.00

av
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Avhandlingen baseras på följande delarbeten

I. Gatenholm.B, Brittberg.M. Neuropeptides: important regulators of joint homeostasis *Knee Surgery Sports Traumatology Arthroscopy. 2019 Mar;27(3):942-949*

II. Gatenholm.B, Gobom.J, Skillback.T, Blennow.K, Zetterberg.H, Brittberg.M. Peptidomic analysis of cartilage and subchondral bone in OA patients. *European Journal of Clinical Investigation. 2019 May;49(5):e13082*

III. Gatenholm.B, Lindahl.C, Brittberg.M, Stadelmann VA. Spatially matching morphometric assessment of cartilage and subchondral bone in osteoarthritic human knee joint with micro-computed tomography. *Bone. 2019 Mar;120:393-402.*

IV. Gatenholm.B, Lindahl.C, Brittberg.M, Simonsson.S. 3D bioprinting with chondrocytes into an osteoarthritic chondral lesion based on patient specific 3D CAD model. *Manuscript under revision for Cartilage.*

V. Gatenholm.B, Lindahl.C, Forsholm.A, Ekholm.J, Brantsing.C, Brittberg.M, Lindahl.A, Simonsson.S. Cartilage tissue formation was degraded by osteoarthritic extracellular matrix micro particles and prevented by 3D bioprinting. *In Manuscript.*

VI. Gatenholm.B, Lindahl.C, StadelmannVA, Brittberg.M. Study of Osteoarthritic knee joints: Correlation between pain, Quality of Life and 3D Cartilage Morphology. *In Manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Abstract

Osteoarthritis (OA) is the most common joint disease, causing disability in middle-aged and elderly patients worldwide and imposing a huge socioeconomic burden. OA of the knee joint is a major cause of joint pain and, along with back pain, it accounts for the two most-reported causes of chronic pain. Despite intensive research in the field, knowledge of the genesis of pain and the pathological processes involved in the development of OA is still very limited. In addition to this, the diagnostic tools used today have low sensitivity and are unable to visualize early disease signs. There is a need for a better understanding of the pain genesis in OA and better early diagnostic tools.

The overall aim of this thesis was to elucidate the mechanism of the pain in osteoarthritic knee joints, with the emphasis on the role of biological signalling and detailed mapping of cartilage damage and the subchondral region. We furthermore investigated future potential diagnostic tools and treatment exploring different imaging techniques and 3D bioprinting.

Study I provided an overview of the field of joint pain with special emphasis on neuropeptides. The review concluded that neuropeptides play not only an important role in nociception but also a regulatory role in many biologic processes, such as bone turnover, inflammation and angiogenesis. **Study II** was a pilot study including tissue samples from six patients with OA undergoing total knee arthroplasty (TKA). We developed a method for analyzing endogenous peptides using Liquid chromatography–mass spectrometry (LC-MS) in cartilage and subchondral bone. In **Study III,** we performed 3D imaging and modeling of morphologic changes in the cartilage and subchondral bone of OA patients using equilibrium partitioning of an ionic contrast agent (EPIC) micro computed tomography (CT). We developed a reproducible and semi-automatic method to visualize structural changes in the cartilage and subchondral bone. In **Study IV,** we compared different imaging techniques and used the 3D images rendered to produce a computer-aided design (CAD) model for visualizing the osteochondral lesion and repairing cartilage damage by 3D bioprinting with chondrocytes. The following study (**Study V**) further investigated cartilage damage repair by forming micro-mass pellets using chondrocytes or chondrocyte-derived induced pluripotent stem cells (iPSCs) with or without OA extracellular matrix (ECM). Our last study (**Study VI**) was a clinical prospective study of 47 patients with knee OA undergoing TKA. Patients were pre- and post-operatively monitored with the knee injury and osteoarthritis outcome score (KOOS) and their experienced pain and quality of life were then correlated to morphologic changes in cartilage and subchondral bone determined with EPIC microCT.

This dissertation presents two new methods for the early diagnosis of OA and possible intervention with 3D bioprinting. The interplay between cartilage and subchondral bone, as well as cartilage damage, neuropeptide signaling and pain, was made apparent. These studies may lead to the development of early diagnostic tools for OA with the potential to make a great contribution to the reduction of suffering and health costs associated with OA.

Keywords: Osteoarthritis, pain in knee joints, cartilage lesions, micro-computed tomography, 3D CAD models, neuropeptides

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