

# Endochondral ossification in the damaged joint

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## Impact paragraph

Cartilage is a durable, but flexible tissue that occurs throughout the body. In articular joints, hyaline cartilage comprises a layer that covers the ends of the bones and provides a surface with very low friction that makes movement possible and at the same time functions as a shock absorber. Unfortunately, cartilage has a very low healing capacity. Therefore, damage to articular cartilage is not resolved and often leads to a pathway of joint deterioration and finally osteoarthritis (OA). Articular cartilage lesions are found in up to 62% of the knees of adults without any symptoms of joint pathology.<sup>1</sup> When cartilage degradation becomes symptomatic, or even progresses into OA, this can have an enormous impact on a person's life. Osteoarthritis is a leading cause of disability worldwide and its burden is only expected to increase due to the ageing population and increasing incidence of obesity.<sup>2,3</sup> Furthermore, disabling OA leads to a substantially reduced long-term work participation and is therefore a major economic concern as well.<sup>4</sup> The most frequently applied therapy for end-stage OA is arthroplasty, but the results of total knee arthroplasty (TKA) in working patients are dissatisfying and one third of patients does not return to work after TKA.<sup>5</sup> The lifetime risk of implant revision is increased in younger patients (up to 35% for men in their early 50s).<sup>6</sup> In addition, the median time to revision is significantly shorter in patients who were younger than 60 at the time of TKA.<sup>6</sup> It is thus of great social and economic value to prevent, or at least postpone progression towards end-stage OA and subsequent (early) TKA. Therefore, the main goal of this thesis was to elucidate how the process of endochondral ossification (EO) can be influenced to improve the treatment of damaged cartilage (i.e., focal cartilage defects and OA).

## Conclusion of main findings

The process of EO is an essential factor in cartilage damage and repair. The findings in this thesis confirm that patient characteristics can negatively influence the outcome of cartilage repair surgery. Potentially by impairing the joint homeostasis and increasing joint inflammation and subsequent EO of the repaired cartilage tissue. The work in this thesis underlines the potential of inhibiting inflammation and influencing the EO pathway with the aim to improve cartilage repair and OA treatment by reducing undesired chondrocyte hypertrophy.

## Implications for research

The influence of inflammation and patient characteristics on the outcome of cartilage repair surgery and OA treatment is widely recognized, but still not fully understood.<sup>7,8</sup> The data in this thesis demonstrate that adequate patient selection can improve the outcome of cartilage repair surgery. In addition, the added value of 7T MRI is underlined. The detailed visualization of morphological and biochemical differences (such as increased calcification of repaired cartilage) suggests that inflammation and EO

can influence the results of articular cartilage repair. This shows that innovations in imaging, such as (high-field) MRI, can aid in an increased understanding of the mechanisms of treatment failure and subsequently provide directions to improve treatment strategies. However, the influence of EO on the quality of cartilage repair tissue and subsequent clinical outcome should be further elucidated in prospectively designed studies. Increased knowledge on the use of 7T MRI also provides a way to evaluate articular cartilage non-invasively and at multiple timepoints, facilitating future clinical research on the influence of EO on articular cartilage damage and repair. This future research could elaborate on the work presented in this thesis that describes the potential improvement of ectopic cartilage tissue formation by influencing inflammation and EO via the inhibition of cyclooxygenase (COX)-2. In addition, the chondrocyte hypertrophy-suppressive effect of aggrecan and cartilage oligomeric protein (COMP) without impairing cartilage formation provides an interesting starting point for future studies.

### Implications for individual patients and society

Good surgeons know how to operate, better ones when to operate, and the best when not to operate.<sup>9</sup> This was stated in a BMJ editorial dating back to 1999, but is still applicable. Not performing unnecessary surgical procedures protects patients from avoidable strain. In addition, it decreases hospital costs and all other socioeconomic costs involved with the surgery. Key findings in this thesis increased the knowledge on risk factors and adequate diagnostic tools to detect cartilage defects and (early) OA. Early detection of cartilage damage provides the opportunity to improve the 'patient journey' by starting early with a suitable treatment, preserve a functional joint and prevent loss of mobility in patients. This can subsequently avoid costly procedures in progressed OA such as revision of total knee arthroplasty or socioeconomic costs caused by disability in patients of working age. Furthermore, an increased understanding was obtained on the role of inflammation and EO on the treatment of cartilage damage and OA by the development of the PEA-CXB microsphere. Derived strategies could further elaborate on the inhibition of chondrocyte hypertrophy and inflammation to treat cartilage damage and potentially lead to a reduction of the amount of (early) TKA and subsequent revision TKA. Next to reduced socioeconomic costs, a reduction in the amount of (early) TKA can also decrease secondary (psychological) complaints and improve the quality of life of OA patients.

### Implications for health care professionals

Next to the implications for the individual patient and society described above, the research results presented in this thesis are valuable for health care professionals as well. We found that late and multiple surgeries in older patients decrease the chance of success in focal cartilage repair surgery. This underlines the importance of adequate early treatment of articular cartilage damage to prevent further deterioration of the

joint. This can be achieved by educating primary physicians to recognize patients with possible articular cartilage damage that are suitable for early referral to an orthopaedic surgeon. This might be even more applicable for physical therapists, as in the Dutch health care system, physical therapy is often the first line of treatment for patients with (minor) musculoskeletal complaints. Orthopaedic surgeons can benefit from a timely referral and potentially provide less invasive, joint preserving treatments.

## Communication towards health care professionals

A timely treatment of articular cartilage damage can prevent further deterioration of the joint.<sup>10,11</sup> In addition, the findings in this thesis showed that a timely treatment of cartilage damage decreases the risk of treatment failure and subsequent TKA. To facilitate this timely treatment of articular cartilage damage, primary healthcare providers involved in the treatment of patients with focal cartilage defects or (early) OA have to be taught that early referral can be joint-preserving. To educate health care providers, publishing research results in peer reviewed journals is essential, but is not enough. Medical information is abundantly available on the internet. However, keeping an overview is complex and the abundant information is impossible to interpret and apply for all different health care providers.<sup>12</sup> For the results of this thesis (and other research) to consistently reach all relevant health care providers, communication will have to be improved. In the following years there will have to be significant advancements in the infrastructure of electronic health records. The currently, not directly linked electronic health records of (amongst others) primary physicians, physical therapists and orthopaedic surgeons will have to be linked or integrated so that all health care providers can have the access to relevant information and are provided with adequate feedback on their treatment actions, ideally supported by scientific research. This can be facilitated by the use of a personal health environment in which personal medical data is owned by the patient and can be shared with different institutions.<sup>13</sup>

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