General introduction
INFLAMMATORY ARTHRITIS

The term inflammatory arthritis (IA) describes a group of chronic autoimmune diseases affecting peripheral and axial joints. IA is characterized by an influx of inflammatory cells, such as macrophages, lymphocytes and granulocytes in joints. This causes pain and stiffness, and may finally result in cartilage/bone destruction and bone formation. The inflammatory process itself is often reversible, but joint destruction is not. IA diseases commonly lead to reduced mobility, functional impairment and reduced quality of life and hence result in high socioeconomic costs for society (1, 2). Early and appropriate treatment is thought to prevent disease persistence, cartilage/bone changes and reduction of functional impairment (3, 4).

The two most common forms of chronic inflammatory arthritis are Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) (figure 1).

RA is a chronic inflammatory joint disease characterized by symmetrical polyarthritis. It typically affects the synovium in small hand and feet joints with a proliferation of synovial tissue and, if not treated adequately, destruction of cartilage and bone. Patients experience joint pain, joint swelling and functional disability. The disease affects about 0.5-1% of the population in the industrialized world. RA has a peak incidence between the fourth and sixth decade, and women are affected two to three times more frequently than men (3). Traditional RA therapy includes anti-inflammatory treatment with systemic glucocorticoids as well as disease-modifying drugs (DMARDs). To date, methotrexate (MTX) is still the most commonly used DMARD, and it continues to be the gold standard of therapy for rheumatoid arthritis. More recently, biological compounds targeting TNF-α and other inflammatory cytokines, B-cells or T-cells have been used successfully to treat RA patients with inadequate response to MTX (3).

AS is a chronic inflammatory disease characterized by inflammatory back pain, limited motion of the spine and sacroiliitis. Peripheral arthritis and enthesitis may also be prominent features (5). Clinical symptoms of AS usually start at an early age.

Figure 1. Structures in the joint and their involvement in RA and AS, respectively. Adjusted from Nature Reviews Rheumatology volume 13, pages 731–741 (2017)
(between 20-40 years) and men are more often affected than women. The exact pathogenesis of AS has yet to be elucidated. Enthesitis plays a central role in AS, both in the axial and peripheral skeleton. Synovitis seems to be less prominent in AS compared to RA (5).

Moreover, bone formation (e.g., syndesmophytes and ankylosis) is a hallmark of AS due to local osteoblastic activity and is related to the functional loss and stiffness. The relationship between inflammation and bone formation in AS is still unclear. Patients with AS are treated with non-steroidal anti-inflammatory drugs (NSAIDs), which stabilize disease activity over time and can reduce progression of structural bone changes (6). More recently, with the introduction of biologicals such as anti-tumor necrosis factor (anti-TNF) therapy, more effective treatment of AS has become possible.

RA and AS have in common that plain radiographs are still the gold standard of imaging in clinical care for detection and monitoring of bone/cartilage changes. The disadvantage of this imaging technique is that synovitis and (active) inflammation is not shown, and these 2D images can miss bone changes over time. Especially in case of AS, radiologic changes appear and change slowly over time, causing a delay in the diagnosis based on radiographs (in years) (7). Consequently, radiographic treatment monitoring only allows long-term observation of potential progression of bone changes. Moreover, not all patients necessarily show bone changes over time. It is known that RA and AS are geno- and phenotypically heterogeneous diseases with different clinical presentation and outcome (8, 9). Treatment regimens containing DMARDs or NSAIDs often have limited response rates and studies found potential different molecular disease pathways within disease groups. Therapies targeting these specific pathways, such as anti-TNFα, anti-CD20 and recently anti-IL17, are emerging rapidly. To apply such new and expensive drugs in the appropriate (sub)group of patients is challenging since it is unknown which patients are most likely to respond to such therapies. Advanced and sensitive imaging techniques may be able to fulfill the clinical needs for early diagnosis of RA and AS, and to optimize therapeutic efficacy.

Positron emission tomography (PET) is a sensitive imaging technique that visualizes functional tissue changes on the (pico)molecular level by targeting binding sites (10). The PET system has a 360° ring that detects pairs of gamma rays emitted after annihilation of a positron-emitting radionuclide. These radionuclides often have a short half-life such as Carbon-11 ($^{11}$C; half-life of 20 minutes) or Fluorine-18 ($^{18}$F; half-life of 109 minutes). With good manufacturing practice (GMP)-compliant radiochemical procedures, radionuclides are linked to the actual molecule of interest. After intravenous injection, the radiolabeled ligands (radiopharmaceutical) can be detected and quantified with the PET scanner. The combination of high specific activity and scanner sensitivity to radioactivity implies that one only needs
micro- to nanomolar amounts of the molecule of interest to investigate molecular processes in vivo. Quantitative PET procedures are well-established and help to reduce observer variability. Taken together, once the molecular targets of disease and its treatment are known, PET may help to detect disease and to predict and monitor the therapy response. Alternatively, PET may help to elucidate the disease process. With the introduction of the hybrid technique PET-CT, the molecular (PET) information can be localized more precisely using computed tomography (CT).

PET is already integrated into daily clinical practice in the field of oncology for diagnosis, staging and follow-up (11, 12), but its application for IA is relatively new (13). In the second chapter of this thesis the current status of PET in peripheral IA is outlined.

OUTLINE OF THE THESIS

In this thesis, different aspects of PET in IA are explored. First, a systematic literature review is presented about the position of PET in imaging and monitoring of peripheral IA in chapter 2.

Subsequently, the thesis is divided into two parts. In the first part the potential (additional) value of PET imaging to support the diagnosis of RA or AS, is investigated. In chapter 3 the radioactive tracers, \[^{18}\text{F}\]FDG (glucose metabolism), (R)-\[^{11}\text{C}\]PK11195 (macrophages) or \[^{18}\text{F}\]Fluoride (osteoblastic activity) are investigated to determine which is most suitable to image patients with active AS. In chapter 4 two new generation TSPO PET tracers for arthritis imaging in RA patients are investigated, which showed better imaging characteristics in a preclinical setting than (R)-\[^{11}\text{C}\]PK11195.

In the second part, PET imaging is used to investigate its potential value for treatment monitoring. In chapter 5 B-cell imaging with PET is used to investigate if this technique has predictive value for the therapeutic efficacy of Rituximab in RA. The therapeutic effects of anti-TNF on bone formation in AS patients are examined with \[^{18}\text{F}\]Fluoride PET in chapter 6. In chapter 7 PET with radiolabeled F8-IL10 is used to visualize the in vivo biodistribution and targeting of this potential new drug for RA.

The results and most important findings of the chapters are summarized and discussed in chapter 8.
REFERENCES


