Peri-prosthetic interface tissue around aseptic loosened prostheses: not waste, but a potential therapeutic target?

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INTRODUCTION

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Clinical problem

Total joint replacement (TJR) is an effective surgical intervention for end-stage joint diseases as osteoarthritis and rheumatoid arthritis. Annually approximately 28.000 total hip (THA) and 24.000 total knee arthroplasties (TKA) are being performed in The Netherlands.[1] These numbers increased in the last 5 years and is expected to increase even more due to the rising incidence of obesity and a more active lifestyle of the elderly.[1, 2] The survival-rates of THA and TKA show consistent results with failure of only 5 -10% after 10 years and up to 20% of revisions at 20 years follow-up.[3-6] Particularly in younger, more active patients the long-term survival of TJRs is reduced compared to the elderly population (older than 65 years).[3-8] Revision surgery consists of removal of the loosened components and peri-prosthetic interface soft tissue, sometimes augmenting cortical and spongious bone loss with allograft bone, and subsequent insertion of new components. Large bone defects, caused by both osteolytic lesions as well as stress shielding create not only a technical surgical challenge to fixate new implant components, but may also cause intraoperative fractures during removal of the implant. Consequently, these revision THA and TKA surgeries are often highly demanding for the patient and can be associated with complications, hence creating new morbidity, particularly in elderly patients with a poor general health condition.[9-11] Additionally, the clinical and functional results of extensive revision arthroplasty surgery are less favourable compared to primary arthroplasty surgery.[12-14] Therefore, therapies less demanding than this extensive revision surgery or even prevention of extensive bone loss during the loosening process would improve quality of patient care.

Aseptic loosening

Aseptic loosening is reported as a major factor limiting the long-term survival of TJRs, accounting for about 50% of THA revisions and 30% of TKA revisions.[1, 15, 16] Aseptic loosening refers to a process during which stable and osseointegrated implants become loose as the bone surrounding the implant is resorbed. This process is regulated by a complex interaction between both biomechanical factors (i.e. stress shielding) and biological factors (i.e. response to wear debris particles through bone signalling at cellar levels).[17, 18] Particulate wear debris, continuously generated by articulating motion at the bearing surfaces, has been implicated as one of the primary causes initiating peri-prosthetic bone loss and implant loosening.[17, 19, 20] Wear debris can be phagocytized by various cell types, triggering a continuous localized peri-prosthetic inflammatory response through the production of inflammatory mediators. These inflammatory mediators create a microenvironment that favours osteoclast formation and subsequently peri-prosthetic bone resorption. The rate of peri-prosthetic bone loss may vary between patients due to differences in the properties and amount of particulate wear debris, different patterns of

biomechanical failure of artificial implants and differences in the individual host immune response which can be related to an individual genotype.[21-27] Therefore, evaluation of individual biological responses is possibly essential to intervene with the process of aseptic loosening.

Peri-prosthetic interface tissue

During the process of aseptic loosening a loose connective fibrous-like tissue develops at the interface between an implant and the bone bed. This so-called peri-prosthetic interface tissue exhibits a heterogeneous cellular composition that generally includes monocyte/macrophage lineage cells (macrophages, foreign body giant cells, and osteoclasts), fibroblasts, endothelial cells, osteoblasts and lymphocytes.[28, 29] Most of these cell types are able to phagocytize wear debris particles and secrete a number of proteolytic enzymes as well as pro-inflammatory and osteoclastogenic cytokines. Proteolytic enzymes, such as matrix metalloproteinases (MMP's), can directly degrade demineralized collagen matrix.[30] The pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 and 6 (IL-1, IL-6), provoke cellular proliferation, stimulate osteoclast activity and/or decrease osteoblast function and thereby disrupt the homeostasis of bone metabolism.[17, 20, 31] Bone metabolism is governed by a delicate balance between bone formation by osteoblasts and bone resorption by osteoclasts. This process is tightly regulated by local and endocrine factors. In normal bone metabolism there is a balance between levels of osteolytic and osteogenic cytokines. In aseptic loosening, this balance is disrupted resulting in a net bone loss around the implant.[32]

Most studies on peri-prosthetic interface tissue focus on the relation between the local production of cytokines and enzymes and their effect on the peri-prosthetic osteolytic process. Histological examination reveals a high inter- and intra-sample variation in both cellular and cytokine profiles within the peri-prosthetic interface tissue, which may represent different stages of loosening in different topological areas.[33-36] This heterogeneity is probably due to the variable biological, mechanical, and material microenvironments along the bone-implant interface.[33, 36-38] Histological evidence also indicates that peri-prosthetic interface tissue is not a tissue with solely bone "destructive" properties. Bone remodelling around the implant has been shown by the presence of intramembranous formation of osteoid, and the production of immature bone with poor quality.[39, 40] Furthermore, several cell types within the peri-prosthetic interface tissue have been shown to produce osteoblast specific proteins [41] as well as to exhibit an increased expression of several bone morphogenetic proteins (BMPs)[42], which are regulators and potent inducers of osteoblast differentiation.[43] The local increase of osteogenic proteins, BMPs and bone remodelling around the implant may indicate that osteogenesis also takes place in peri-prosthetic interface tissue.

Targets for treatment

Through the years, many efforts have been made at improving the quality of primary joint replacements and thereby reducing the prevalence of aseptic loosening and the potential need for revision surgery. For example, alternative bearing surfaces have been developed which significant reduced the amount of wear.[44-47] However, regardless of these efforts, aseptic loosening still persists. Therefore continued research into new therapies to treat aseptic loosening is necessary to prolong the lifetime of prostheses. So far, studies aiming at identifying targets for treatment of aseptic loosening have primarily focused on interfering with the osteolytic process. However, only partial inhibition of bone resorption could be achieved in studies using non-steroidal anti-inflammatory drugs (NSAIDs) and/or antibodies to specific osteolytic mediators.[48-50] The results of the clinical use of bisphosphonates to treat bone resorption in aseptic loosening were inconsistent.[51, 52] Alternatively, therapeutic agents targeted at improving bone formation in the peri-prosthetic osteolytic areas are also likely to countermeasure the osteolytic process. However, hardly any studies exist on this topic. In fact, the role of peri-prosthetic interface tissue cells in bone formation is yet even unclear.

Outline of this thesis

The objective of the research described in this thesis is to increase the knowledge on the biology behind the process of aseptic loosening. For this purpose, we aim to study the loosening process from three different biological perspectives, according to the following research questions:

1. Does the cellular content of peri-prosthetic interface tissue shed new light on the mechanism of implant loosening?
2. Do peri-prosthetic interface tissue cells possess osteogenic potential, which can ultimately be used to prevent or slow loosening?
3. Does the individual host immune response relate to prosthesis migration, which can ultimately predict loosening?

The first research question is addressed in **Chapters 2** and **3**. In **Chapter 2**, an overview of currently known cellular mechanisms involved in aseptic loosening, based on *in vitro* findings, is given. The cellular mechanisms are further explored in **Chapter 3**, where the cellular characteristics of peri-prosthetic interface tissue samples are studied by determining cell-specific gene expression patterns and using immunohistochemistry. In **Chapters 4** and **5**, the second research question is addressed. In **Chapter 4**, the possibility to enhance bone regeneration, by intervening with signalling pathways which are important for osteogenic differentiation, is studied in human and murine cell lines. Results from this study are used in

Chapter 5, where we investigate whether cells derived from peri-prosthetic interface tissue are capable of differentiation into the osteoblastic lineage. The third research question is addressed in **Chapter 6**, where we investigate the relation between non-specific cytokine (innate immune) responses and the early migration of prostheses. Finally, **Chapter 7** concludes this thesis with a summary and general discussion including future directives on the treatment of aseptic loosening.

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