The Infrapatellar Fat Pad Is A Key Focal Point For The Development Of Arthrofibrosis Following Total Knee Arthroplasty


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Introduction: Total knee arthroplasty (TKA) is one of the most successful orthopaedic procedures that reliably alleviates pain and restores function in patients who have degenerative knee joint diseases. A recent audit revealed that annually 70,000 TKA are performed in England and Wales (NHS) and >1.5 million worldwide (Gallo, J., et al. 2013). Arthrofibrosis, defined as abnormal scarring of the joint in which the formation of dense fibrous tissue and tissue metaplasia prevents normal range of motion, represents a significant clinical challenge and develops in 3-10% of patients undergoing TKA. However, what triggers the proliferation of extensive scar tissue formation in patients with arthrofibrosis is unclear. No prophylactic intervention is available and therefore treatment for arthrofibrosis is restricted to aggressive physiotherapy or revision surgery. Every year hundreds of patients with a total knee replacement (TKR) undergo revision surgery due to stiffening of the knee (arthrofibrosis). This surgery puts the patient at risk of complications such as risks from undergoing an anaesthetic, infection, bleeding, damage to structures around the knee and pain amongst others. Revision surgery also comes at a great cost to the NHS: surgeon’s time, theatre use, theatre staff, equipment, postoperative high dependency bed, physiotherapy etc. Improving our understanding of the mechanism driving the disease would allow us to identify novel therapeutic targets to limit or reverse the disease therefore reducing the number of revision TKAs, improving patients’ quality of life and mortality, and benefitting the NHS financially.

The aim of this study was to macroscopically and histologically compare and contrast the tissue architecture and composition of the synovial membrane and infrapatellar fat pad of patients undergoing primary TKA and revision TKA, to improve our understanding of the pathophysiology of arthrofibrosis.

Methods: Tissue (synovial membrane and infrapatellar fat pad) was collected from consenting patients (n=10/group) undergoing their first (primary) TKA or second (revision) TKA. Patients undergoing revision surgery were identified as non-fibrotic or fibrotic (n=5/group) at the time of surgery. Tissue was fixed in formalin and embedded in paraffin blocks. Sequential sections were prepared and stained for picrosirius red (total collagen) collagen I, collagen III and alpha SMA (fibroblasts). The percentage area positive for collagen I, collagen III, picrosirius and alpha SMA was determined by acquiring n=10 randomly selected high powered fields (Nikon inverted microscope) and quantifying using percentage area positive staining using image analysis software (NIS Elements). Differences between the groups were analysed by Mann Whitney U tests.

Results: Macroscopically, infrapatellar fat pad from primary TKA appeared to be homogenous, fatty, non-fibrotic tissue. In contrast, infrapatellar fat pad from revision TKA appeared to be dense, pigmented,
fibrotic tissue (figure 1 upper panel). Histologically there was a significant increase in the percentage area positive for picrosirius red (20.1% vs 75.6%, p<0.001) (figure 1 lower panel, figure 2), collagen I (13.6% vs 72.3%, p<0.001) and collagen III (11.4% vs 16.9%, p<0.01) in the infrapatellar fat pad of revision TKA compared to primary TKA. In contrast there was no significant difference in the percentage area positive for picrosirius red (37.9% vs 47.6%, p=0.31), collagen I (34.4% vs 39.2%, p=0.89) or collagen III (14.2% vs 14.4%, p=0.89) in the synovial membrane of primary TKA compared to revision TKA. Finally, the percentage area positive for alpha SMA was found to be higher in the revision TKA group compared to the primary TKA group in both the fat pad (0.7% vs 5.1%, p=<0.001) and synovial membrane (1.7% vs 5.5%, p=0.01). Significantly when revision TKA patients were stratified into fibrotic and non-fibrotic there was still a significant increase in the percentage positive area for all markers in the infrapatellar fat pad of non-fibrotic and fibrotic revision TKA compared to primary TKA. In addition, a non-statistically significant trend towards an increase in the percentage positive area for all markers was seen in fibrotic revision TKA compared to non-fibrotic TKA suggesting an ongoing fibrotic process (picrosirius red shown in figure 3).

**Discussion:** There is a significant difference in the architecture and composition of the infrapatellar fat pad of patients undergoing revision TKA over primary TKA, with an increase in both extracellular matrix deposition and an increased number of alpha SMA positive mesenchymal cells. These changes are unique to the infrapatellar fat pad and are not reflected in the synovial membrane, suggesting the fat pad may be a key focal point for the development of arthrofibrosis post TKA. Surprisingly, regardless of whether revision TKA patients are identified as fibrotic or non-fibrotic at the time of surgery, there are statistically significant differences in fibrotic markers compared to tissue collected from patients undergoing primary TKA.

**Significance:** Our data characterizing the architecture and composition of tissue from patients undergoing primary TKA and revision TKA provides us with an increased understanding of the pathophysiology of arthrofibrosis, with evidence that the fat pad is a key structure. This data facilitates further work to elucidate mechanisms driving the disease and identify novel therapeutic targets, with the potential to dramatically reduce the number of revision TKAs performed.