

# Synovial inflammation in patients with different stages of knee osteoarthritis

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## Abstract

The synovium is an intra-articular mesenchymal tissue and essential for the normal joint function. It is involved in many pathological characteristic processes and sometimes specific for this distinctive tissue. In this study, we refer to synovial proliferative disorders according to the stage of osteoarthritis (OA) disease. Forty-three patients with knee OA were treated in the Department of Orthopedics and Traumatology, Emergency University Hospital of Bucharest, Romania, in the last two years. In all cases, we used at least five criteria for the knee OA: knee pain, knee joint tenderness, no palpable warmth over the knee, stiffness, erythrocyte sedimentation rate and C-reactive protein levels. In all the cases the synovial tissue was selected by the orthopedic surgeon. X-ray examination was taken in every case of the affected joint. Patients who were considered to have early OA underwent arthroscopic synovial biopsy of the symptomatic joint. Synovial tissue samples from patients with late OA were obtained at the time of knee joint arthroplasty. Microscopic examination in early osteoarthritis revealed for more than half of patients with synovial biopsy through arthroscopic technique having synovitis lesions with mononuclear infiltrates, diffuse fibrosis, thickening of the lining layer, macrophages appearance and neoformation vessels also. The synovitis seen in advanced OA knees tends to be diffuse and is not mandatory localized to areas of chondral defects, although an association has been reported between chondral defects and associated synovitis in the knee medial tibio-femoral compartment. The overexpression of mediators of inflammation and the increased mononuclear cell infiltration were seen in early OA, compared with late OA.

**Keywords:** synovitis, osteoarthritis, mediators of inflammation, cell infiltration.

## Introduction

Knee osteoarthritis (OA) is the most common form of arthritis, and is the single most important cause of disability in older adults and sometimes even in young patients. First, the synovium and also the bone and cartilage are involved in pathological processes that lead to progressive joint degeneration [1, 2].

There is a multifactorial etiology of OA that might include both systemic and local biomechanical factors. Systemic factors include age, sex, estrogen levels, racial and genetic susceptibility, bone density, and many nutritional factors. The occurrence of synovitis after trauma to the knee joint may result in progressive patello-femoral chondropathy [3, 4].

The synovial membrane in osteoarthritis (OA) shows a more or less 'normal' appearance with no increase in the thickness of the intimal cell layer or significant cellular reaction.

While synovitis is common in advanced osteoarthritis (OA), its prevalence and severity in patients with early or mild OA are uncertain [5–7].

Although osteoarthritis (OA) is commonly described as a non-inflammatory joint disease, synovial inflammation is increasingly recognized as contributing to the symptoms and progression of OA. Synovial histological changes include synovial hypertrophy and hyperplasia with a big

number of lining cells often accompanied by infiltration with lymphocytes [8].

Starting from other studies [9, 10] of the quality of the synovium, in our study we aimed to evaluate the synovial inflammation degree by macroscopic, X-ray examination and histological findings in patients with early or late knee OA.

## Materials and Methods

Samples of synovial tissue were obtained from 43 patients with knee OA that were treated in the Department of Orthopedic and Traumatology, Emergency University Hospital of Bucharest, Romania, in the last two years. Gender ratio was 33 females and 10 males with the age between 49 and 76-year-old.

Patients with anterior knee pain for at least one year, who were considered to have early OA, underwent to X-ray examination and arthroscopic synovial biopsy of the symptomatic joint. The three articular compartments of the knee joint were explored. Synovial tissue samples from patients with late OA were obtained at the time of knee joint arthroplasty.

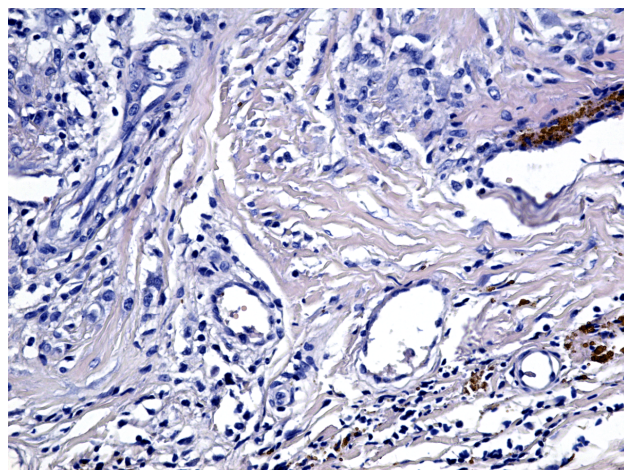
In all cases, we used at least five clinical and laboratory criteria for the knee OA diagnosis: knee pain, knee joint tenderness, no palpable warmth over the knee, stiffness, erythrocyte sedimentation rate and C reactive protein levels.

In all the cases, the synovial tissue was selected by the orthopedic surgeon, after the patients previously signed an informed consent. Efforts were made to ensure that tissue was selected from areas demonstrating gross synovial hypertrophy. If hypertrophy was not apparent, tissue samples were randomly selected.

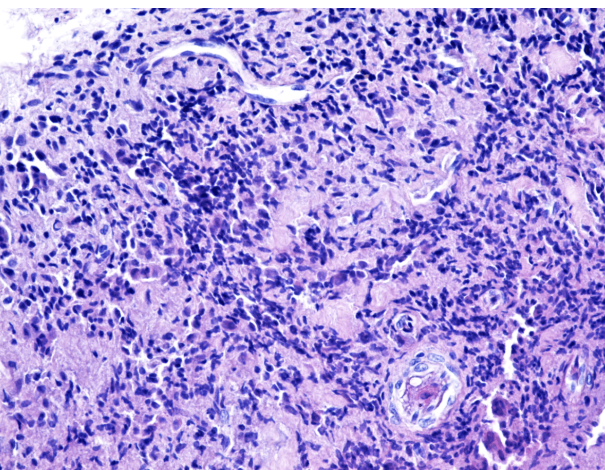
All histological sections were examined without knowledge of the clinical details of the case, including the diagnosis.

Tissue fragments were placed in 10% buffered formalin taking care that the volume of the formalin solution exceeds 10 times the volume of the sample. Then, the tissue was embedded in paraffin using the standard technique. The paraffin blocks were sectioned using the microtome to 5 µm thick sections, which were then stained using the classic Hematoxylin and Eosin (HE) technique.

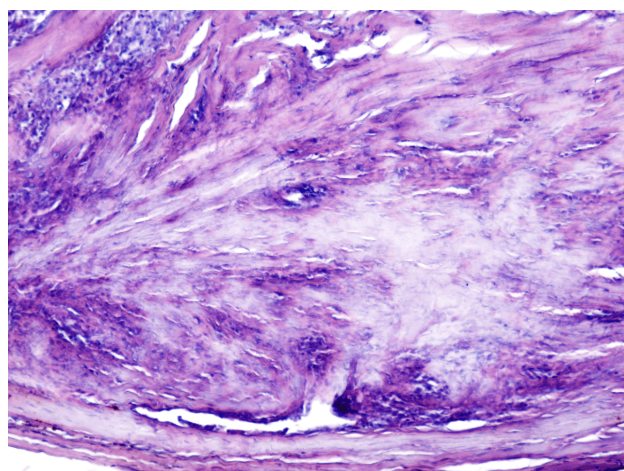
HE-stained sections were evaluated for the presence of intimal cell hyperplasia, increased vascularity, fibrin deposition, diffuse lymphocytic infiltrate, perivascular lymphocytes, lymphoid follicles, plasma cells, diffuse fibrosis and perivascular fibrosis.



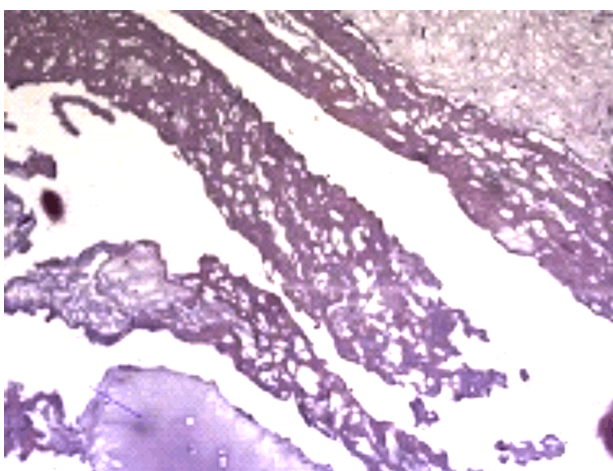
**Figure 1** – Synovial with an altered structure, by the presence of a chronic moderate inflammatory and numerous neoformation vessels (HE staining, ×200).



**Figure 2** – Area of synovial membrane, strongly infiltrated with macrophage and lymphocyte cells (HE staining, ×200).



**Figure 3** – Intensely thickened synovial by abundant deposit of hyaline and collagen fibers (HE staining, ×100).



**Figure 4** – Fibrin deposit, areas of necrosis and degenerated cartilage (HE staining, ×100).

At this stage of osteoarthritis, most patients accused anterior knee pain while going up and down the stairs, symptoms that also appears when the level of physical

There were processed in the laboratory also synovial fluid samples taken at surgery time.

## Results

### Microscopic changes in early osteoarthritis

Histological study of synovial tissue revealed more than half of patients with synovial biopsy through arthroscopic technique having synovitic lesions. With, thickening of the lining layer, proliferation of the lining cells, mononuclear infiltration especially with macrophages. The presence of small blood capillaries with turgescient endothelium shows the neo-formation aspect and highlights the proliferation process of synovitis (Figures 1 and 2).

Different degrees of fibrosis were present in the synovial connective tissue (Figure 3).

Knee's articular cartilage has no perichondrium, thus we found cartilage structural alterations in all patients, synovial changes being present especially in areas of chondral defects (Figure 4).

activity increases, without any deformities of the knee or biomechanical axis deviation.

In the early stage of OA, the X-ray findings are



minimal or absent, due to the minimal changes of cartilage, thus for no changes of the subchondral bone.

### Microscopic changes in late osteoarthritis

There was noticed an extensive synovitis in patients who underwent total knee replacement. Synovial inflammation was not confined to patients with extensive radiographic joint damage or advanced stage disease. The synovitis seen in advanced OA knees tends to be diffuse and it is not mandatory localized to areas of chondral defects, although an association has been reported between chondral defects and associated synovitis in the knee medial tibio-femoral compartment. Histologically, the increase of collagen fibers, the presence of lymphoid cell infiltrates can be finding, near the increase of neoformation vessels (Figures 5 and 6).

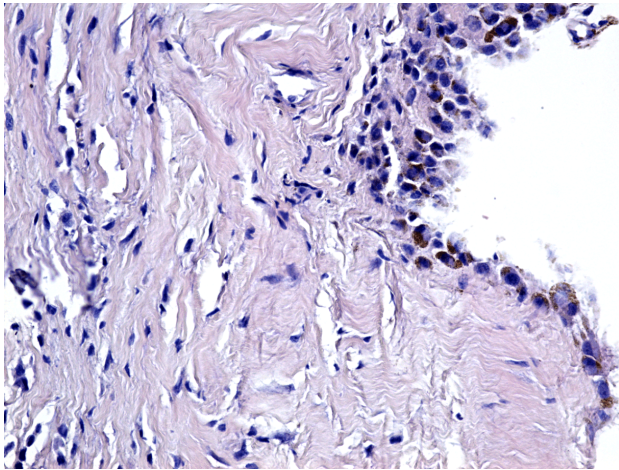
Patients in advanced stages of OA have pain all around the knee more pronounced on the medial side and sometimes this pain wakes them up at night. They accuse different degrees of knee stiffness with creaks or

crunches as they move. It can be seen that the knees look swollen because of the osteophytes around the sides of the joint or caused by extra fluid in the joint.

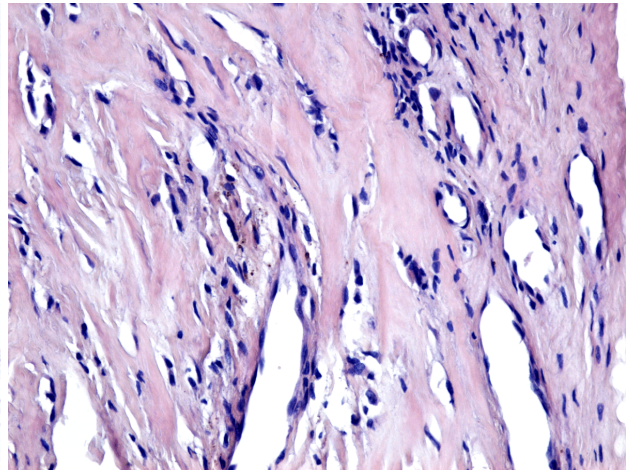
### Imagistic in late osteoarthritis

In this stage of OA, the following radiographic changes can be identified: narrowing of the joint space, osteophytes, subchondral sclerosis, appearance of subchondral cysts and subluxation of the joint particularly in advanced OA (Figure 7). X-ray findings of this stage of OA show not only the degenerative aspect, of the articular surface, but also the proliferative aspect. The advanced fibrosis of the synovitis, which also involves the joint capsule of the medial tibio-femoral compartment and the presence of osteophytes, explains the proliferative aspect of OA and also helps to subluxation of the knee joint.

Magnetic resonance imaging (MRI) shows joint effusion, meniscal disruption subchondral signal changes, and synovitis, which appears in advanced OA (Figure 8).



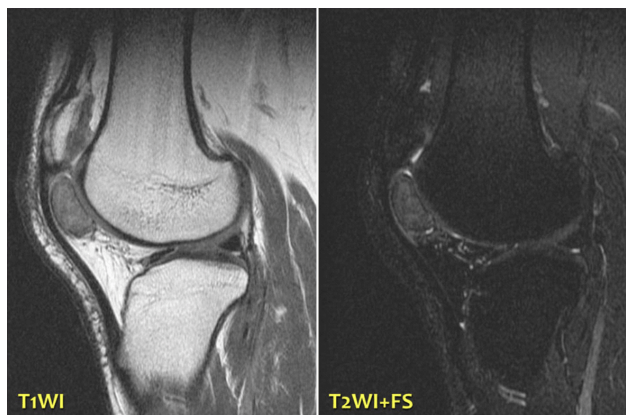
**Figure 5 – Synovial membrane with numerous hypertrophied cells and disordered placement collagen fibers, present in the late stages of the disease (HE staining,  $\times 200$ ).**



**Figure 6 – Microscopic aspect of non-specific chronic synovitis, with numerous congested blood vessels and collagen deposits (HE staining,  $\times 200$ ).**



**Figure 7 – X-ray showing late OA with chronic synovitis and calcification.**



**Figure 8 – MRI of a late knee OA.**

### Discussion

OA is considered not only a degenerative, but also a proliferative disease, due to the chronic inflammatory response to the cartilage damage of the joint surface. Regarding the old publications in osteoarthritis appeared

to be a relatively normal synovium, accompanied by areas of fibrosis, hyper-vascularization and fragments of cartilage. Otherwise, recent studies demonstrates both obvious changes of the synovial membrane and synovial fluid in osteoarthritis disease that varies depending on the severity of the condition [11–13].

Our study corresponds with other research papers and demonstrates the early histological modifications of the synovium, like mononuclear cells, macrophages infiltration, accumulated collagen fibers and neoformatted vessels, in the beginning phase of OA. Radiological aspects in this phase of OA is normal or with minimal modification. Any small damage of the cartilage surface induces an inflammatory response by the overexpression of pro-inflammatory mediators, like IL-1, TNF $\alpha$  (tumor necrosis factor alpha), and VEGF [14].

The observation of the synovial tissue from patients with early OA demonstrated more features of inflammation than late OA. OA synovial tissues have also been shown to produce vascular endothelial growth factor and other angiogenic factors that promote neovascularisation of subchondral bone [15]. These neoformatted vessels are more fragile and their damage leads to hemorrhage contributes to the increase of the inflammatory response.

Interleukin-1 receptor antagonist is frequently detected in the synovial membrane of normal patients, but both TNF $\alpha$  and IL-1 are rarely detected [16, 17]. Proliferation of new blood vessels, and increased expression of several critical molecules, including cytokines, angiogenic factors, adhesion molecules, and inducible COX are characteristic of chronic synovitis in inflammatory arthritis. Even the early stage of OA is distinguished by a high level of production of inflammatory cytokines IL-1, IL-6, TNF $\alpha$ , infiltration of mononuclear cells, thickening of the synovial lining layer and fibrosis. The explanation for the apparent difference is unclear, but may be related to differences in patient and tissue selection, or to the quantification techniques that were employed. Involvement of synovitis in the pathophysiology of osteoarthritis inflammation is evident but may not be always the primary mechanism that generates it [18, 19].

The overexpression of mediators of inflammation and the increased mononuclear cell infiltration is seen in early OA, compared with late OA. Isolated fibroblast-like synoviocytes were functionally similar in both, early and late OA, consistent with microenvironmental differences in the synovial tissue during different phases of OA. These aspects are very important in the treatment of patients with early OA [20].

All these mechanisms lead to recurrent inflammatory response, cartilage damage aggravation. This vicious circle of pathophysiology leads to clinical, radiological and histological aspect of the OA and the better knowledge of the pathology opens new opportunities in the treatment.

## ✉ Conclusions

The extent of the synovial inflammatory lesions is important for the clinical outcome of the patient. Our study revealed that early osteoarthritis is accompanied by a localized synovial inflammation in areas of chondral defects, while late osteoarticular knee inflammation determines diffuse chronic synovitis. This diffuse fibrotic process involve closer joint structures, the appearance of new vessels explains also the proliferative aspect of the disease. Early X-ray examination shows the normal aspect of the joint or minimal modification of OA, like subchondral sclerosis. In advanced stages of OA, the

diffuse fibrotic process in synovial tissue may involve the joint capsule, which explains the limitation of the joint mobility and the subluxation of the joint.

## Conflict of interests

The authors declare that they have no conflict of interests.

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