sciendo Romanian Journal of Orthopaedic Surgery and Traumatology, Volume 5, Issue 1, January-June 2022. pp:35-41
doi:10.2478/rojost-2022-0007

Accepted: December 8th 2022

REVIEW

Gene expression and molecular aspects in osteoarthritis of the knee - review of literature

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Abstract

Gonarthrosis is one of the main causes of pain and limitation of physical activity in elderly patients. The diagnosis is established based on the clinical and radiological examination, and the treatment consists of non-surgical measures. The final stage of gonarthrosis is treated surgically and consists of total knee arthroplasty.

The molecular study in gonarthrosis aims to identify patients with early stages of arthrosis, with reversible potential, who can benefit from etiological treatment and non-pharmacological measures to slow down the evolution of the disease or even reversibility. Total knee arthroplasty is a surgical intervention with the role of reducing the symptoms and restoring the functionality of the affected joint.

Total knee arthroplasty remains the surgical intervention of choice in the case of patients in the final stage of the evolution of the disease with very good functional outcome.

Keywords: knee osteoarthritis, gene expression, molecular, review

Introduction

Gonarthrosis is one of the main causes of pain and limitation of physical activity in elderly patients. The knee is the most frequently affected anatomical site by osteoarthritis in patients aged > 65 years [1]. The incidence of gonarthrosis is increasing considering the aging process of the population [2]. Knee OA is characterized by multiple changes in the cells of the synovial membrane, articular cartilage, subchondral bone, ligaments and menisci, synovial fluid, all changes being based on a change in gene expression.

Although arthrosis is a condition specific to the phenomenon of aging and is called primary gonarthrosis, it can also start in young patients in the form of secondary gonarthrosis, the most common causes being represented by systemic inflammatory

diseases, joint infections, post-traumatic or congenital dysplasia [3].

The diagnosis is established based on the clinical and radiological examination, and the treatment consists of non-surgical measures such as weight loss, physical therapy, the use of non-steroidal anti-inflammatory drugs, analgesics, intra-articular infiltrations with steroidal anti-inflammatory drugs or visco-elastic substances. The final stage of gonarthrosis is treated surgically and consists of total knee arthroplasty. The surgical indication is independent of the patient's age and considers the presence of radiological changes of gonarthrosis and the failure of all non-surgical treatments to improve the pain and functional outcome.

Considering the degree of impairment of physical activity and the increased incidence of gonarthrosis with a major impact on the quality of life, identifying potentially reversible etiological factors becomes a public health problem.

Traditionally, knee OA has been regarded as a degenerative joint disease that affects the joint cartilage, leading to its destruction over time with the adjacent consequences. Currently, gonarthrosis is regarded as a disease of the entire joint or even a systemic disease, because it can be influenced by numerous local or systemic factors. Patients with pre-symptomatic stages of gonarthrosis show molecular and structural changes [4].

Gonarthrosis-molecular characteristics

Fan et al. described the pathogenesis of gonarthrosis as a series of genetic changes involving the articular cartilage, synovial membrane, subchondral bone, tendons, muscle tissue, menisci and infrapatellar fat [5]. The creation of a pro-inflammatory environment is based on the accumulation of macrophages in the synovial tissue, which leads to the secretion of pro-inflammatory cytokines that favor the persistence of synovitis and the degradation of articular cartilage [6].

In a study published in 2020, Zeng et al. highlighted a series of cytokines and adipokines secreted by Hoffa fat that maintain and worsen the pro-inflammatory environment at the knee level [7].

More than 1500 genes involved in the regulatory phenomena that lead to the appearance of KOA have been described until present. Of these, Steinberg J et al. presented the importance of the expression of 6 genes with the potential for accelerated degradation of articular cartilage, isolated by gene sequencing from the articular cartilage of patients who benefited from total knee arthroplasty. The involved genes are represented by MMP1, MMP2, MMP13, IL6, CYTL1 and APOD [8].

Molecular classification of gonarthrosis

In a review published in 2021, Zhongyang L et al. divided gonarthrosis into 4 stages from a molecular point of view [9].

The PRE-KOA stage refers to the asymptomatic phase, without imaging changes of gonarthrosis, structural changes or lesions evident arthroscopically and considers the identification of risk factors. Among the risk factors, obesity should be mentioned, which, in addition to the mechanical effect on the joint surfaces, is characterized by an increased secretion of leptin and resistin in the serum. The two components are responsible for activating the innate immune system and stimulating the expression of pro-inflammatory cytokines, which, as afore-mentioned, have the potential to destroy articular cartilage [10,11].

Female gender is another risk factor for KOA. In a study that included 842 female patients, Sowers et al. demonstrated that the increased serum level of estradiol together with its metabolite 2-hydroxyesterone has a direct association with the risk of KOA [12].

Joint trauma is incriminated as having a role in the early development of arthrosis lesions [13]. Fractures involving the articular surface have a direct role by affecting joint congruence, but also meniscus injuries or complete injuries of the cruciate and collateral ligaments by affecting joint biomechanics. In addition to the biomechanical aspects, the molecular studies highlighted the presence of two molecules with an important role in the arthrogenesis of these patients, cartilage oligomeric matrix protein (COM) and C-telopeptide of type II collagen (CTX-II).

Table 1*. Risk factors for PRE-KOA and specific biomarkers*

RISK FACTORS FOR KOA	BIOMARKERS
OBESITY	Leptin Serum resistin
JOINT INJURY	COMP CTX-II
AUTOIMMUNE DISEASE	MAT2β-AAb
FEMALE SEX	2-hydroxyestrone Estradiol

EARLY-KOA stage

The definition and classification of this stage was proposed by Luyten et al. and includes the clinical examination and imaging data. Early-KOA must fulfill all 3 listed criteria, knee pain, KL grade < 2, cartilage lesions diagnosed by arthroscopy or MRI, or subchondral or meniscal lesions diagnosed by MRI [14]. Molecular alteration is the consequence of changes in gene expression, more precisely through the inhibition of some protein coding transcripts by microstructures called micro RNAs (miRNAs). miR-140 and miR-210 are the main miRNA structures that influence local homeostasis. Thus, miR-140 can maintain bone and cartilage homeostasis, but since it presents a low value in the synovial fluid in patients at this stage, the prognostic value is low [15,16]. Also, miR-210 is considerably upregulated in patients with early and late stage KOA compared to healthy individuals [17].

Other biomarkers with promising results in the prognosis of KOA are IL-17 and IL-15.

IL-17 shows increased levels in the synovial fluid of patients with gonarthrosis and decreases in the final stages of the disease's evolution [18]. IL-15 shows a distribution similar to IL-17, with increased values in the synovial fluid in patients at the onset of the disease and low values in the final stages [19].

Progressive KOA

In general, the arthritic disease has a slow evolution over time with progressive worsening despite the applied treatment, because until this moment there is no treatment to stop the evolution of the disease. According to the molecular profile, Zhongyang et al. classified the stage of progressive KOA into four subtypes.

Cartilage Degradation-Driven Subtype

It is based on the degradation of articular cartilage and especially of Col-II, which is why an increased level of CTX-II was strongly associated with the severity of gonarthrosis [20]. Besides this, CTX-II represents an independent risk factor for total knee arthroplasty [21]. CTX-II can be dosed from the patient's urine.

Other molecules with prognostic value are degradation products of Col-II and are mentioned in table 2.

Bone Remodeling-Driven Subtype

Bone remodeling at the subchondral level occurs because of the alteration of the bone production/ resorption process of osteoclasts and osteoblasts. C-telopeptide of Col-I (CTX-I), N-telopeptide of Col-I (NTX-I) were highlighted within the molecular description of this stage [22]. Other biomarkers with a role in the progression of gonarthrosis are represented by TRAP5b, bone alkaline phosphatase (ALP), and the serum value of N-terminal collagen type I extension propeptide (PINP) [22].

Inflammation Driven Subtype

In the case of KOA, the inflammation is one with a long evolution, chronic, with specific clinical manifestations. Regarding the inflammatory activity, the most studied biomarkers are IL-1β and TNF-α, whose values correlate directly with symptoms and radiological changes [23]. Other biomarkers with an important role in the progression of arthritic disease are represented by IL-6, IL-1, chemokines CCL3 and CCL4, but also the increased level in the synovial fluid of CD163 and CD14, along with the CRP value [24].

Pain Driven Subtype

Pain is the main symptom that leads to the presentation of the patient to the orthopedic surgeon. In addition to the complications of gonarthrosis, such as limitation of joint mobility, flexion contractures, deviation of the axis in valgus or varus, pain remains the predominant symptom that leads to the pronation of diagnostic and therapeutic measures. The main biomarkers studied are represented by the well-known CRP, which can highlight the inflammatory component of pain, but can also be used to monitor the response to non-steroidal anti-inflammatory treatment, bradykinin and calcitonin gene related peptide (CGRP) [25,26].

END-STAGE KOA

It is represented by patients with Keller Lawrence stage IV KOA, with pain not relieved by non-steroidal anti-inflammatory treatment and complications such as flexion contractures, ligament laxity and severe limitation of physical activity. Although the treatment of these patients is surgical by arthroplasty with total knee prosthesis, a biomarker with a role in risk stratification and disease progression was highlighted, NLR (neutrophil-lymphocyte ratio) [27].

***Table 2**. Molecular stage of KOA and specific biomarkers*

MOLECULAR STAGE OF KOA	BIOMARKERS
PRE-KOA	Leptin Serum resistin COMP CTX-II MAT2β-AAb 2-hydroxyestrone Estradiol
EARLY KOA	miR-140 miR-210 miR-19 miR-122 miR-146a miR-186 miR-223 miR-486 IL-17 IL-15
PROGRESSIVE KOA	
CARTILAGE DEGRADATION-SUBTYPE	Urinary CTX-II C2M C2C Coll 2-1
BONE REMODELING-SUBTYPE	C-Col 10 CTX-I

	NTX-I C1M
INFLAMATION-SUBTYPE	TRAP5b ALP PINP IL-1β IL-1Ra TNF-α IL-6 CCL_3
PAIN-SUBTYPE	CCL_4 Hs-CRP CRPM Bradykinin CGRP NGF
END STAGE KOA	NLR (neutrophil-lymphocyte ratio) let-7e

Discussion

The molecular study in gonarthrosis aims to identify patients with early stages of arthrosis, with reversible potential, who can benefit from etiological treatment and non-pharmacological measures to slow down the evolution of the disease or even reversibility. Total knee arthroplasty is a surgical intervention with the role of reducing the symptoms and restoring the functionality of the affected joint, but at the same time it is burdened by a series of local and general complications. Also, part of the patients who benefit from total knee arthroplasty continue to present post-operative pain with important limitation of mobility. The molecular study aims to identify the specific biomarkers that lead to the appearance of symptoms and the future use of specific therapy with the potential to reverse the lesions or stop them.

Conclusion

Although more studies at the molecular level and a better understanding of this pathology are needed, the moment of the patient's presentation to the doctor remains an essential condition to be able to intervene in early stages with the potential for reversibility. Although a series of medicinal agents with potential reversibility have been used, the associated risks have exceeded the benefits of the therapy. Thus, the future in the treatment of gonarthrosis is personalized therapy, adapted to each patient, replacing the current concept of standardized treatment for all patients.

Total knee arthroplasty remains the surgical intervention of choice in the case of patients in the final stage of the evolution of the disease with very good functional outcome.

Conflicts of interest
The authors state no conflict of interest.

Acknowledgements
None.

Sources of Funding
None.

Disclosures
None.

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