PRIVATE HIGHER EDUCATION INSTITUTION
«KYIV MEDICAL UNIVERSITY»

PUZANOVA O.H.
BATUSHKIN V.V.

RHEUMATIC DISEASES:
BASICS OF DIAGNOSIS

TEXTBOOK

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TEXTBOOK

Best wishes to my students!

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The Standards and Guidelines for Quality Assurance in the European Higher Education Area include ensuring the quality of training and teaching, creating a wide base of advanced knowledge and competencies, improving curricula, and using flexible learning paths and innovation in forms and methods of providing educational sevices. This is consistent with the principle of continuing education and confirms the need to improve methodological support on arduous practical issues, especially at the undergraduate stage, in the residency and primary care. Among such tasks, diagnostics of rheumatic diseases occupies a special place.

The book's content corresponds to the requirements of the curriculum in the discipline «Internal medicine» for medical students of higher education institutions. Both history of the description of rheumatic diseases and anatomy and physiology of the muscluloskeletal system are presented briefly, whereas semiotics, methodology and practical aspects of the examination and evaluation of a patient with muscluloskeletal symptoms or suggested rheumatic disease are described in details. Relevant international guidelines are also given.

Educational material is submitted in accordance with the principles of practical orientation, optimal sufficiency, and the approaches such as systemic scientific, propaedeutic, consistent, autonomous, competence-based, and evidence-based. Complex didactic material is presented by theoretical information, demonstrated examples, questions and review test items for self-control. There are 25 tables and 23 figures in the book.

Intended for medical students of the 5th and 6th years and postgraduates of an English-language form of training, as well as for continuing medical education of the general practitioners-family doctors, internists, rheumatologists, and orthopedic traumatologists.

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Introduction

Persistent damage to the *musculoskeletal system*'s components – joints, muscles, ligaments, tendons, bones – is a leading feature of *rheumatic diseases*. More than 120 such diseases are known, they are common, often difficult to diagnose, severe or life-threatening.

Pathogenetic basis of most rheumatic diseases is chronic autoimmune inflammation of the *connective tissue*, which is an important structural and functional component of almost all organs connecting them with each other. A number of rheumatic diseases are on the verge of different medical specialties (orthopaedics and traumatology, cardiology, neurology as well); in addition, musculoskeletal disorders can be manifestations of cancer, infection, endocrine diseases, etc.

In general, 30% of the population suffers from joint and back pain. The most common joint disease is *osteoarthritis (OA)*, which is also a major cause of pain and disability worldwide. It ranks globally among the 50 most common sequelae of diseases and injuries, affecting over 250 million people or 4% of the world population. The most common arthritis in middle-aged men is *gouty*. As of 2017, almost 20 million people worldwide were living with *rheumatoid arthritis (RA)*, with over a million new cases diagnosed each year. Much attention is currently paid to the problems of timely diagnosis of *spondyloarthritis (SpA), connective tissue diseases (CTDs)*, and *systemic vasculitides*, which more often affect people of young and middle age increasing the risk of developing main *non-communicable diseases (NCDs,* such as cardiovascular and chronic kidney disease), infectious and lymphoproliferative diseases as well.

Competence in the methodology of diagnosing musculoskeletal and rheumatic disorders is of great importance. It implies advanced knowledge and skills in propaedeutics, i.e. semiotics and diagnostic approaches (including those adopted at various medical schools), mastering patient examination and evaluation, as well as ability to interpret laboratory findings. All of the above will improve the quality of exam preparation and further practical work.

According to the requirements of the curriculum in the discipline «Internal medicine» for medical students, the continuing medical education (CME)'s principle, and taking into account such a global trend as population ageing, a special attention should be given to the *age-related* musculoskeletal disorders (frailty, etc.) and their prevention. In general, *arthritis* is the leading cause of disability in people over the age of 55, while *osteoporosis* is the most common reason for fractures in the elderly. *Fractures* are the main cause of morbidity and mortality related to trauma in people older than 65 years in the USA: in 2014, fractures were revealed in 28,7% of such adults (in total 29 million cases), which caused 33 thousand deaths in a year. In 2015, 2 million new cases of fractures were recorded, and in 2025, 3 million are predicted. The term *sarcopenia*, which was proposed 30 years ago to describe the age-related disorder and later

substantiated as a syndrome associated with an increased risk of falls and physical frailty, is currently recognized as one out of five key risk factors of morbidity and mortality of the elderly.

The concept of CME implies improvement of methodical support in the field of managing patients with muscluloskeletal disorders, especially at the undergraduate stage, in the residency and primary care. This textbook is aimed at improving the self-training of senior medical students and graduates (residents, etc.), and may be useful for postgraduate education of general practitioners-family doctors, internists, rheumatologists, orthopedic traumatologists as well.

Brief history of the description of rheumatic diseases

Joint diseases have been known since the 4th century BC, which is suggested by the fact that 18 Hippocratic aphorisms are dedicated to them. The term *rheuma* was introduced in the 1st century AD, and its meaning resembled the Hippocratic *catarrhos* (i.e. flow, spreading): Galen was the first to use the term ***rheumatism*** to refer to joint diseases. In the 17th century, the concept of rheumatism *as a systemic musculoskeletal syndrome* was introduced by the Parisian physician G.Baillou who claimed that «what arthritis is in a joint that is exactly what rheumatism is in the whole body» [30], and «the English Hippocrates» T.Sydenham began the identifying discrete diseases from *mix of rheumatism and gout* (since this name was also used indiscriminately to refer to arthritis). He distinguished from gout an acute polyarthritis «chiefly attacking young and vigourous» and, using the designation St Vitus' dance, described ***rheumatic chorea*** (this word derived from Greek for dance), which is currently known as Sydenham's chorea. The first to study ***rheumatic carditis*** were the London physician D.Pitcairn (1788, unpublished), the Ukrainian physician H.Volkovinsky (1817) and the French physician J.-P.Bouillaud (1840). Pitcairn wrote that «the persons subject to rheumatism were attacked more frequently than others with symptoms of an organic disease of the heart», then Bouillaud concluded that «in the great majority of cases of acute articular rheumatism with fever, there exists in a variable degree the rheumatism of the serofibrinous tissue of the heart» [35, p. 1]. Given the contribution of G.Sokolsky («On Rheumatism of Heart Muscle Tissue», 1836, Moscow), this malady was also called *Sokolsky-Bouillaud disease*. The diagnostic criteria for rheumatic fever were first developed by O.Kissel (published in 1940, Moscow) and T.D.Jones (1944, Boston).

As for ***gout*** (*gutta* in medieval medicine was a synonym for the Greek *podagra*), little of significance was learned about it between the 4th century BC and the 17th century, when the Dutch scientist A. van Leeuwenhoek described the microscopic appearance of urate crystals from a tophus. Two centuries later, the English physician A.Garrod demonstrated urate in subcutaneous tissue and articular cartilage in cases of gout, assuming that it might result either from a loss of renal excretory capacity or from increased formation of uric acid (1859), and postulated that gout attack resulted from the precipitation of sodium urate in a

joint or adjacent tissue (1879). Today, gout is considered a chronic systemic inflammatory disease that not only affects joints and kidneys, but also increases the cardiovascular risk.

The cornerstone of rheumatology, ***RA***, was first described as *goutte asthenique primitive* by A.-J.Landré-Beauvais (1800, Paris), then by B.Brodie (1819, London) who recognized that it began as a *synovitis* that led to destruction of articular cartilage. The term RA was proposed by A.Garrod (1858) for the name of the «joint disease having some of the external characters of rheumatism»; then J.-M.Charcot (1867, Paris) made «excellent clinical differentiations among gout, rheumatic fever, RA…and may have been the first to recognize that RA is not rare» [35, p. 2]. Concerning serological diagnosis, of great importance was the finding by E.Waaler (1940, Oslo) that sheep erythrocytes incubated with rabbits' anti-sheep cell serum were agglutinated by some rheumatoid sera. The sensitized sheep erythrocytes agglutination reaction was developed as diagnostic test by H.Rose (1948, New York, NY). Its most known variation *latex-test* uses a suspension of polystyrene latex particles coated with human gamma globulin.

The ***juvenile chronic arthritis*** was distinguished by G.Still (1897, London) who pointed out such features of the polyarthritis in adolescents as fever, lymphadenopathy, splenomegaly, pericariditis, cervical spine lesion, and growth retardation. In 1971, the other English physician E.Bywaters first reported Still's disease in adults. Currently, this disease is assigned to the SpAs.

Interest in ***SpA*** was stimulated by the works by V.Bechterew describing «spine numbness with its curvature as a special form of the disease» (1892-1899, St. Petersburg), A.Strümpell (1897, Erlangen) and P.Marie (1898, Paris). The association of *iritis* with an ***ankylosing spondylitis (AS)*** was mentioned by V.Bechterew (1893) and assumed by E.Kunz and E.Kraupa (1933), the German ophthalmologists. With AS, the male predominance was recognized by F.Glaser (1901, Berlin), the radiologic finding of *sacroiliitis* was first reported by W. Krebs (1934, Aachen), the association with *aortic insufficiency* – by P.Kulka (1957, Boston). In 1973, the strong epidemiologic evidence of a genetic predilection to the developing SpA in *HLA-B27* carriers was obtained by L.Schlosstein (Los Angeles) and D.Brewerton (London). This served as an incentive to study the pathogenetic role of histocompatibility antigens in rheumatic diseases.

No less interesting is the role of infection. First descriptions of arthritis following sexual contact and diarrhea were done by Hypocrates and Galen, respectively. The history of another SpA – ***reactive arthritis (ReA)*** – was considered together with gonococcal arthritis from the first descriptions of arthritis related to urethritis or blenorrhagia in Europe (P. van Forest, 1507; F.Swediaur, 1784) to clear distinction between these diseases in the USA (V.Wrigh, W.Reed, 1964). In England, at the very beginning of the 19th century, T.Whateley presented a case report on the arthritis with urethritis following asymptomatic period and not representing gonococcal disease, then B.Brodie made «classic description of the classic triad of ReA» in several men with

recurrences of urethritis, conjunctivitis and arthritis (currently known as *Reiter's triad, syndrome or disease*) [13]. The American authors wrote that M.Stoll was the first to report the association between dysentery and arthritis in soldiers (in 1776, during the American Revolutionary War), while A.Cooper coined the *concept of a relationship between infection and arthritis* primarily of the lower limb (1824). However, in 1916, the French physicians N.Fiessinger and E.Leroy and the German doctor H.Reiter independently published their descriptions of *conjunctivo-urethro-synovial syndrome* in the French troops and in a German officer, respectively. In 1948, I.Paronen described 344 cases of arthritis following Shigella dysentery in Finland during World War II. In 1969, P.Ahoven et al. introduced *the concept of ReA* as arthritis that develop soon after or during infection elsewhere in the body, but in which the microbe cannot be recovered from the joint.

Note that «in the English literature, it is generally called *Reiter's disease*, and in North America and Latin America, it is called *Reiter's syndrome*» [13]. In Germany, the use of this term as «unfortunate for historical and didactic reasons» is not approved [23, p. 135].

As for ***OA***, then the English physician W.Heberden distinguished nodes on the fingers from tophi (1802) and the French physician G.Bouchard described identical nodes proximally (1884). But it was A.Garrod (1907) who introduced the modern usage of the term OA and related Heberden's nodes to this disease. The generalized OA was described in 1952 by J.H.Kellgren.

In 1876, the first cases of ***osteitis deformans*** were reported by the famous English surgeon and pathologist J.Paget. Much later, in 1950, the French rheumatologist J.Forestier distinguished ***ankylosing spinal hyperostosis*** (or diffuse idiopathic skeletal hyperostosis) from spondylosis.

The earliest definite descriptions of ***scleroderma*** were published in the 1840s by several English and French physicians, and in those same years, some skin manifestations of ***lupus erythematosus (LE)*** were described. A century later, the term *diffuse collagen diseases* was introduced by P.Klemperer (1942, NY) who suggested both systemic lupus erythematosus (SLE) and scleroderma «acute and chronic maladies that are characterized autonomically by generalized alterations of the connective tissue» [35, p. 3]. Despite of rapid acceptance of the concept of collagen diseases (or *collagenoses*), it was gradually replaced by the term and concept of ***connective tissue diseases*** suggested by W.E.Ehrlich (1952, Philadelphia) [50, p. 22].

Important findings from the study of manifestations of SLE, systemic sclerosis (SS), dermatomyositis (DM) and polymyositis (PM) in the second half of the 19th century and the first half of the 20th century are shown in **Table 1**. As we see, *LE cell phenomenon* with SLE was described in the same year and country (1948, USA) as the specific serology finding with RA, while *antinuclear antibodies (ANA)* were first detected almost ten year later in Switzerland.

Table 1.

Study of manifestations of connective tissue diseases in the 19th -20th centuries

Contribution	Author(s)
Description of an *erythema-«butterfly»*	F. von Hebra, 1845, Vienna
Introduction the designation *sclerodemie*	E.Gintrac, 1847, Bordeaux
Using the term *lupus erythemateux* to identify a skin disease	P.Cazenave, 1851, Paris
Descripting *vasospastic phenomenon* with scleroderma	M.Raynaud, 1862, Paris
Description of death due to *renal failure* in scleroderma*	H.Auspitz, 1863, Vienna
Use of the term *lupus erythemateux* to designated skin lesions combined with fever and pneumonia	M.Kaposi, 1872, Vienna
Description of *myocardial fibrosis* with scleroderma**	C.Westphal, 1876, Berlin
Introduction of the term *polymyositis*	E.L.Wagner, 1886, Leipzig
Introduction of the term *dermatomyositis*	H.Unverricht, 1891, Tartu
Pointing out the *consistent association* between Raynaud's phenomenon and scleroderma	J.Hutchinson, 1899, London
Description of the *pulmonary fibrosis* with scleroderma	A. von Notthafft, 1899, Munich
Assumption of the *pathogenetic association* between dysphagia and skin lesions with scleroderma	S.Ehrmann, 1904, Vienna
Description of many *visceral features of SLE* (under the name of exudative erythema)	W.Osler, 1895-1904, Baltimore
Detection of the developing *calcinosis* with scleroderma	G.Thibierge, R.Weissenbach, 1910, Paris
Adding *verrucous endocarditis* to the visceral signs in SLE	E.Libman, B.Sacks, 1923, NY
Description of the exacerbation effect of sunlight and the *«wire loop»* glomerular lesions	G.Baehr et al., 1935, NY
Pointing out the association between *DM* and *cancer*	R.Bezecny, 1935, Prague
Establishing the association in scleroderma of calcinosis with the Raynaud's phenomenon, esophageal dysfunction and teleangiectasia***	T.Prosser, 1942, London
Introduction the term *progressive systemic sclerosis*	R.Goetz , 1945, Capetown
Detection of *LE cell* in bone marrow aspirates in acute SLE; demonstration of the LE cell formation in peripheral blood	M.Hargraves, 1948, 1950, Rochester
Developing the method to detect the LE cell inducing factor such as *ANA*	A.Miesher, 1956, Lausanne; G.Friou et al., 1958, West Haven

Notes. *The association between renal failure and scleroderma was confirmed by H.Moore and H.Sheehan (1952, Liverpool). **Myocardial fibrosis was recognized as a manifestation of scleroderma by S.Weiss (1943, Boston). ***This was coined as CREST-syndrome by R.Winterbauer (1964, Baltimore).

Let's say how ***systemic vasculitides*** were first described. Previously called *polyarteritides,* they are rare but life-threatening diseases. The first certain case was reported by K.Rokitansky in a pathologic study of aortic aneurysms (1852, Vienna). Having found aneurysms in most of the medium size and small arteries in one published case, A.Kussmaul and R.Maier (1866, Freiburg) proposed the term *periarteritis nodosa.* The term ***polyarteritis nodosa*** was coined by E.Ferrari (1903, Trieste) who characterized a patient with severe arteritis without aneurysms.

Granulomatosis with polyangiitis (GPA) was described first by H.Klinger (1931, Berlin), then in greater detail by F.Wegener (1936, Breslau) whose name was later given to this disease. J.Churg and L.Strauss (1951, NY) reported allergic granulomatosis with bronchospasm and eosinophilia, currently known as ***eosinophilic granulomatosis with polyangiitis (EGPA).***

The most common systemic vasculitis in adults is ***giant cell arteritis (GCA)*** described in 1890 by J.Hutchinson and rediscovered in 1932 by B.Horton in the Mayo clinic (Rochester). Its representatives made a great contribution to improving the diagnosis of GCA and its connection with the development of blindness and aortic aneurysm in the elderly. The association between GCA and ***polymyalgia rheumatica*** was first suggested by J.Paulley (Ipswich, UK) in 1956.

So, the accumulation of descriptions of musculoskeletal disorders and systemic rheumatic diseases (such as CTDs, SpAs, systemic vasculitides, etc.), as well as analysis, synthesis, and systematization of the findings occurred from the 17th century, and especially actively from the middle of the 19th century to the middle of the 20th.

As for ***arthroscopy,*** it was first performed by the Japanese physician Takagi (1918), the first paper on it in English was published by P.Kreuscher (1925), but the technique was not utilized until the first partial meniscus removal performed by M. Watanabe (1957).

Concerning ***evidence-based approach*** to diagnosis and prevention of rheumatic diseases, it is postulated that the first evidence to support the hypothesis of an immune pathogenesis of rheumatic fever was the discovery of *antistreptolysins* by E.Todd (1932, London) [35]. In 1938, advancing *the concept of clinical epidemiology*, the American virologist J.Paul studied the path of rheumatic fever's outbreaks in the small communities of the NY city and developed the concept of preventive medicine as clinical discipline and science.

The term ***rheumatologist*** is recent, coined in 1940 by B.Comroe, preceding the introduction of the term ***rheumatology*** in his textbook edited by J.Hollander in 1949. However, a number of *national and international medical associations* in the field were found, including the German Society for Rheumatology (DGRh, 1927), the American College of Rheumatology (ACR, 1928), the European League Against Rheumatism (EULAR, 1947), etc. Based on the best evidence, they provide *guidelines* on the diagnosis and management of the rheumatic diseases.

The ***Ukrainian medical school*** is known for its considerable achievements in the field of rheumatology by *O.Kissel* (who first proposed the diagnostic criteria for rheumatic fever), *V.Vysokovych* (thanks to his contribution to the study of the physiology of connective tissue), *T.Yanovsky* (one of the Kyiv therapeutic scientific school's founders), *L.Dmytrenko* (she described a «velvet tone», which is an auscultatory sign of rheumatic endocarditis with a mitral valve lesion), *I.Horbachevsky* (who discovered the xanthine oxidase enzyme), *V.Nasonova* (whose more than 500 works were devoted to the study of rheumatic fever, RA, CTDs, OA, gout, etc.), *V.Vasilenko* (who described the fourth heart sound, proposed a classification of heart failure, led the development of methods for determining the severity of mitral and aortic valve defects, and so on), *O.Hrytsyuk* (the founder of the Republican rheumatology center, known also for his work on hemostasis), *I.Handzha* (who studied CTDs, pulmonary vasculitis, etc.) and many others.

Questions for self-control:

1. What means «rheuma»? Who introduced the terms «rheumatism», «rheumatology», and «rheumatologist»? When they were introduced?
2. Who introduced the term «rheumatoid arthritis» and when?
3. Which of the following terms is currently accepted: (a) collagenoses, (b) diffuse connective tissue diseases, (c) systemic connective tissue diseases, (d) connective tissue diseases?
4. What do you know about the descriptive period of the developing diagnosis of rheumatic diseases? When did the evidence-based approach to their diagnosis begin?
5. What international medical associations in the field of rheumatic diseases do you know?

Brief information on the anatomy and physiology of the musculoskeletal system

There are three types of bone junctions: synarthroses, symphyses, diarthroses. ***Synarthroses*** are fixed junctions; these are divided into *syndesmosis* (e.g., skull sutures, connections of spinous processes of the vertebrae) and *synchondroses* (rib-sternal junctions, etc.). ***Symphyses*** are semi-movable cartilage-type junctions (like a pubic fusion); ***diarthroses*** are freely movable junctions, or *true synovial joints* in which the bones are separated by hyaline cartilage. Of interest is the sacroiliac joint, the posterior part of which is syndesmosis, and the anterior one is the true synovial joint.

The shape of the articular surfaces distinguish *flat joints* (e.g., intercarpal, sacroiliac joints), *spherical* (hip joint, shoulder joint), *elliptical*, or *condyloid* (radiocarpal, ulnocarpal, metacarpophalangeal (MCP), and metatarsophalangeal (MTP) joints), *block-shaped* (elbow joint, interphalangeal joints), *wheel-shaped* (joint of the 1st cervical spine), *condylar* (knee joint, temporomandibular joint),

saddle-shaped (the articulation between the trapezium carpal bone and the 1st metacarpal bone at the base of the thumb).

The articular surfaces of the bones that form the synovial joints are covered with ***hyaline cartilage***, which contains neither vessels nor nerves, but consists of a *matrix* (97%), chondrocytes and chondroblasts. These cells produce glycosaminoglycans (GAGs) and proteoglycans (PGs, primarily *aggrecan*). PGs form complexes with hyaluronic acid and are fixed in a network of *collagen fibers*, which provides the stability of its structure. *Type II collagen* is specific for cartilage and is the primary collagen of articular cartilage. Since the PGs are more susceptible to enzymatic degradation than collagen, then their turnover rate is faster.

Chondrocyte synthetic activity responds to various factors such as *growth factors and cytokines*. The degradation of macromolecules is under the control of proteolytic enzymes (primarily *metalloproteases*), which are synthesized by the chondrocytes. The measurement of *keratan sulfate* serum level is an informative test for PGs' degradation in cartilage.

The function of adult cartilage as an avascular tissue depends on the diffusion of nutrients and electrolytes from the synovial fluid through the matrix, in which interstitial water plays a primordial role. Under routine (physiological) mechanical loads on cartilage, its synthetic activity (i.e. synthesis of PGs) increases, but its structure does not change. Under excessive loads, ***chondrocyte dysfunction*** occurs, cartilage undergoes dystrophic and structural changes (i.e. swelling, branching), loses elasticity and resilience. Namely chondrocyte dysfunction is a key link in pathogenesis of the most common joint disease, such as ***OA***. With OA, the content of GAGs in the cartilage decreases (first of all, it concerns chondroitinsulfates) and depolimerization of PGs occurs. Since monomers bind water worse, collagen absorbs its residue; the matrix swells, and cartilage is cracked.

The anatomical structure of the knee joint is shown in **Fig. 1**. The joint is enveloped in a fibrous ***joint capsule***, which passes into the *periosteum* (covering the cortical layer of the bone) and supports the ***synovial membrane*** – the inner covering of the joint. Synovial membrane consists of three layers (integumentary, collagenous, elastic) and produces fluid in the ***joint cavity***, which may connect with the ***synovial bursa*** located between the tendons and muscles.

With OA, dystrophic changes develop in all joint structures – cartilage (first of all), synovial membrane, joint capsule, ligaments, subchondral bone, and periarticular muscles. The following factors are very important for the pathogenesis of OA: changes in the subchondral bones, fibrosclerotic changes in the synovial membrane, and reactive synovitis.

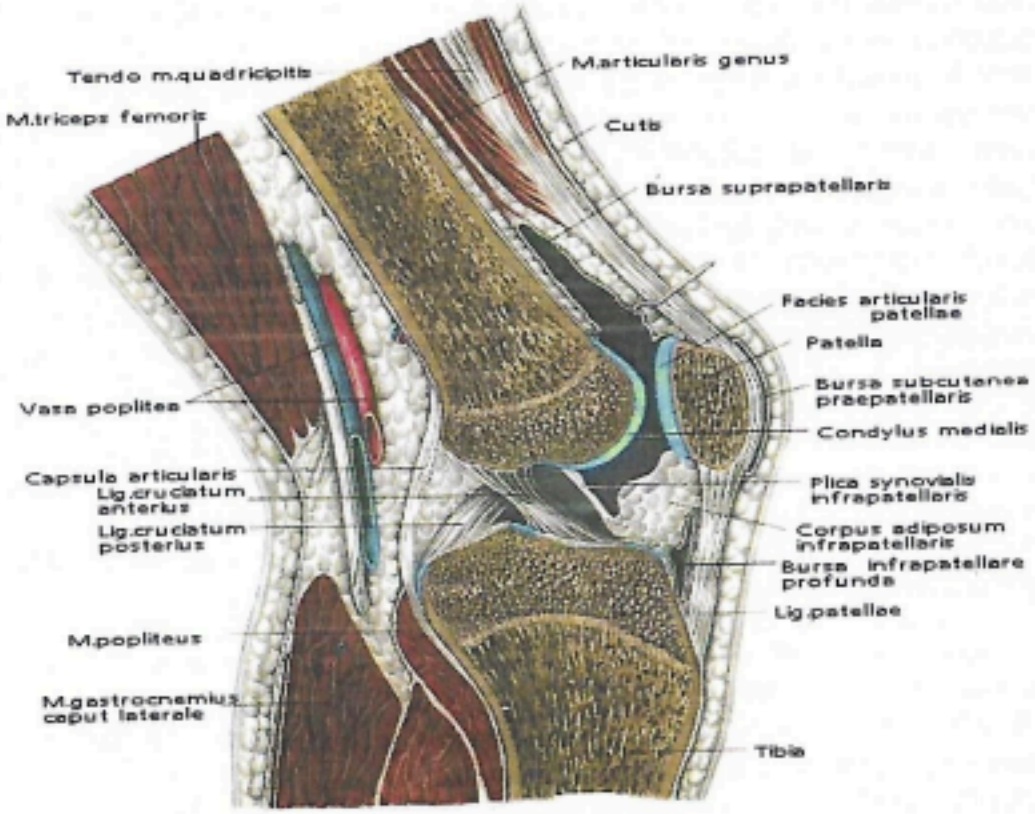
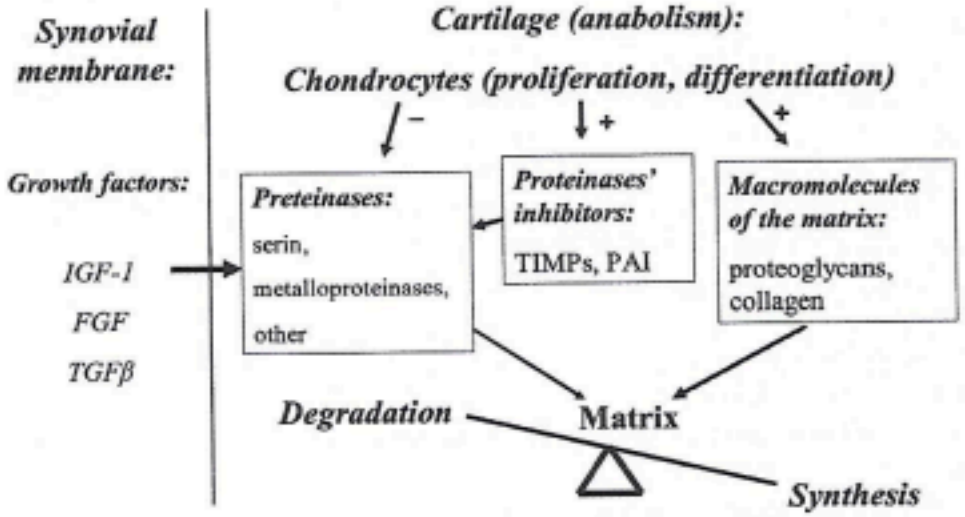


Fig. 1. Anatomical structure of the human knee.

Risk factors for *early development of OA*, in particular of the knee joint, are trauma, excessive sports training (in football, weightlifting, running), overweight and obesity, developmental abnormalities (patella dysplasia, flattening of the lateral femoral condyle), position abnormalities (genu varum, genu valgum, dislocation of the patella, its high standing and lateral displacement), as well as pathological changes in the hip joint, ankle joint, sacroiliac joints and lumbar spine, in the presence of which the mechanical load on the cartilage in femoropatellar and femorotibial joints increases. Nevertheless, the regulation of articular cartilage homeostasis is ensured primarily by *internal factors* (**Fig. 2**) [39, p. 440-444].

Hormones such as somatotropin, prolactin, insulin, estrogens, insulin-like growth factor-1 (IGF-1, or somatomedin C) stimulate fibroblast proliferation (including chondroblast) and collagen synthesis. The latter may be inhibited by glucagon, parathormone, calcitonin, adrenalin and thyrois glands' hormones. Somatomedin C is considered a physiological stimulator of chondrogenesis; its content in blood increases under the action of insulin, prolactin and somatotropin, and decreases under the action of high doses of estrogens and cortisol.



Note: + *stimulation,* − *inhibition.*

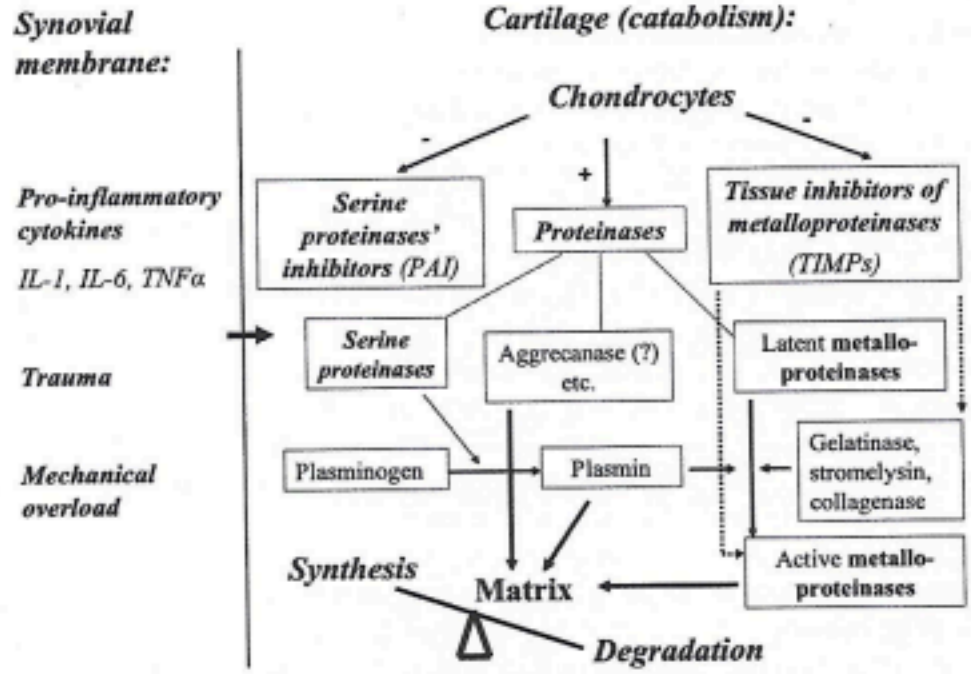


Fig. 2. Factors regulating articular cartilage homeostasis.

Both the synovial membrane and cartilage persistently produce immune protective and aggressive factors – primarily pro- and anti-inflammatory cytokines (under normal conditions – in small and balanced amounts). To aggressive factors belong interleukins IL-1, IL-6, IL-17, IL-23 and tumor necrosis factor alfa (TNFα), metalloproteinases (such as collagenase, stromelysin, gelatinase), activator of plasminogen synthesis. The protective factors are IL-4, IL-10, growth factors IGF-1, TGF-β, FGF (insulin-like, transforming, and fibroblast, respectively), tissue inhibitors of metalloproteinases (TIMPs), and plasminogen activator inhibitor (PAI).

This is both the significant increase of pro-inflammatory cytokines' content (primarily in the joint structures, later in blood) and relative deficiency of endogenous anti-inflammtory hormones such as glucocorticoids (GCs) that occur in ***RA***, leading to development of morning stiffness and other signs of arthritis and systemic inflammation (fever, weight loss, anemia, increasing of the acute phase proteins' content in blood, etc.).

Inflammation of synovial membrane (***synovitis***) is the morphological basis of any arthritis and a common manaifestation of CTDs. With RA, the autoimmune synovitis leads to developing ***pannus*** – vascular-fibrous tissue capable of invasive growth and destruction of cartilage, ligaments, tendons and subchondral bone (*erosive lesions* are its specific symptom). «Crowling» on the cartilage, the pannus replaces it, the joint space narrows, fibrous joint is formed, and eventually ankylosis. With *OA*, the development of synovitis (usually insignificant) is a respond of synovial membrane to its mechanical and antigen irritation by the components of cartilage, bone fragments, osteophytes, calcium salts' crystals, etc.

The influence of synovitis on the cartilage was described by F. Eulderink as follows: «Only numerous joints attacks accompanied by inflammation of synovial membrane are capable of completely cartilage destruction» [39, p. 444]. The fastest destruction of joint structures occurs when infectious agents are introduced into them – i.e., with *infectious (purulent, septic) arthritis*.

Let's speak of **bone** as a connective tissue containing «99% of the body's calcium, 80% of the phosphate and large amount of sodium, magnesium, and carbonate» [35, p. 11]. There are three types of cells in bone (osteoclasts, osteoblasts, osteocytes) and two subtypes of bone (cortical and cancellous). *Cortical (or compact) bone* comprises 80% of the skeleton and is enriched in the long bone shafts. *Cancellous (or trabecular) bone* is flat platelike bone, which contacts intimately with the cells of the marrow cavity; this is enriched in the vertebral bodies, pelvis, proximal ends of the femora (which are all subjects to low energy fractures in the elderly) and is very susceptible to the effects of GCs. Both bone subtypes are continuously renewed by the process of *remodeling* that consists of cycles of bone resorption and bone formation, occurs in discrete skeleton zones (known as *bone remodeling units*).

































































































































