**DRUG NEPHROPATHY**

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**Summary**: *The article presents data on the incidence of chronic kidney disease in rheumatoid arthritis. Kidney damage is common in patients with rheumatic diseases, and can also develop either due to the disease itself or secondary to drugs used in the treatment. For pain relief in patients with rheumatoid arthritis, non-steroidal anti-inflammatory drugs (NSAIDs) are often used. In rheumatoid arthritis, the occurrence of chronic kidney disease depends primarily on the duration of the disease and the nature of the inflammatory process. These data are fully confirmed at the present time. The problem of kidney damage in rheumatoid arthritis is poorly understood and requires further research.*

**Key words**: *rheumatoid arthritis, risk factors, non-steroidal anti-inflammatory drugs, chronic kidney disease.*

**ЛЕКАРСТВЕННАЯ НЕФРОПАТИЯ**

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**Резюме**: *В статье представлены данные о частоте встречаемости хронической болезни почек при ревматоидном артрите. Поражение почек – это частое явление у пациентов с ревматологическими заболеваниями, а также может развиваться либо из-за самого заболевания либо вторичного к лекарствам, используемом при лечении. Для купирование боли у пациентов с ревмотоидным артритом, часто используют нестероидные противовоспалительные препараты (НПВП). При ревматоидном артрите возникновение хронической болезни почек зависит, прежде всего, продолжительность заболевания и характера воспалительного процесса. Эти данные полностью подтверждаются в настоящее время. Проблема поражения почек при ревматоидном артрите мало изучена и требует дальнейших исследований.*

**Ключевые слова**: *ревмотоидный артрит, факторы риска, нестероидный противовоспалительные препараты, хроническая болезнь почек.*

**DORILARNING NEFROPATİYASI**

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**Rezyume** : *Maqolada revmatoid artritda surunkali buyrak kasalligi bilan kasallanish haqida ma'lumotlar keltirilgan. Buyrakning shikastlanishi revmatik kasalliklarga chalingan bemorlarda keng tarqalgan bo'lib, kasallikning o'zi yoki davolashda ishlatiladigan dorilar tufayli ham rivojlanishi mumkin. Romatoid artritli bemorlarda og'riqni yo'qotish uchun ko'pincha steroid bo'lmagan yallig'lanishga qarshi dorilar (NSAID) qo'llaniladi. Romatoid artritda surunkali buyrak kasalligining paydo bo'lishi, birinchi navbatda, kasallikning davomiyligi va yallig'lanish jarayonining tabiatiga bog'liq. Bu ma'lumotlar hozirgi vaqtda to'liq tasdiqlangan. Romatoid artritda buyrak shikastlanishi muammosi yaxshi tushunilmagan va qo'shimcha tadqiqotlarni talab qiladi.*

**Kalit so'zlar**: re*vmatoid artrit, xavf omillari, steroid bo'lmagan yallig'lanishga qarshi dorilar, surunkali buyrak kasalligi.*

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic damage to internal organs. The prevalence of RA is about 0.7%. The annual incidence is approximately 0.02%. The incidence of kidney damage in RA, according to different authors, ranges from 35 to 73% [1], with drug exposure playing a major role.

Currently, in medicine there are a huge number of conditions that manifest themselves in the development of pain and require the use of painkillers. Thus, systematic use of nonsteroidal anti-inflammatory drugs (NSAIDs) can not only slow down the diagnosis of a disease accompanied by pain, but also lead to the development of other, more serious diseases. One of the severe side effects of long-term and uncontrolled use of non-steroidal anti-inflammatory drugs is, along with damage to the gastrointestinal tract, kidney damage.

The main effects of drugs from the NSAID group on the human body include analgesic, anti-inflammatory and antipyretic effects.

The unfavorable prognostic significance of kidney damage in rheumatoid arthritis (RA) is actively attracting the attention of researchers in

recent years [6]. Some clinical variants of kidney involvement in the pathological process in rheumatoid arthritis are observed in most patients [31]. Various types of kidney damage in rheumatoid arthritis have been described, in particular, glomerulonephritis, amyloidosis, vasculitis, as well as iatrogenic forms (analgesic tubulopathies, membranous nephropathy, etc.) [34, 29].

The KDIGO guidelines (2012) define CKD as “impairments in the structure or function of the kidneys that persist for more than three months and have an impact on health

status" [20]. The Association of Nephrologists of Russia (2019) defines CKD as "persistent organ damage for three months or more due to the action of various etiological factors, the anatomical basis of which is the process of replacement of normal anatomical structures with fibrosis, leading to its dysfunction," but all nephrologists agree that in In clinical practice, the diagnosis of CKD "should be established when clinical examination reveals any markers indicating kidney damage that persist for three months or more" [37].

According to some researchers, the development of CKD in RA may be associated with cardiovascular damage to a greater extent than with the activity of RA itself [9]. It is noteworthy that the amount of data on factors contributing to the development of cardiovascular pathology, as well as various types of nephropathies and chronic kidney disease in RA is insufficient, and the available information is scattered and somewhat contradictory [25, 12].

It is noteworthy that in real clinical conditions, such patients may not undergo morphological verification of renal pathology for a long time for a number of objective reasons. Early manifestations of functional renal disorders, especially when they are moderate, do not always attract the attention of clinicians, while the progression of chronic kidney disease (CKD) in RA can be rapid, especially in old age, as well as when associated with cardiovascular pathology [ 7, 10].

Despite modern advances in nephrology and rheumatology, in RA not all links of pathogenesis, as well as risk factors, the modification of which would reduce the rate of progression of renal pathology, have been well studied. Approaches to early detection of renal pathology and assessment of the risk of its worsening in RA have not been sufficiently developed.

The development of renal dysfunction in patients with RA is caused not only by the presence and severity of autoimmune disorders and chronic systemic inflammation, but also by the multiplicity of comorbid conditions, and also, equally important, by the peculiarities of pharmacotherapy - the need for long-term use of potentially nephrotoxic drugs (cytostatics, biological agents, nonsteroidal anti-inflammatory drugs, etc.) [28].

Thus, systematic use of nonsteroidal anti-inflammatory drugs (NSAIDs) can not only slow down the diagnosis of a disease accompanied by pain, but also lead to the development of other, more serious diseases. One of the severe side effects of long-term and uncontrolled use of non-steroidal anti-inflammatory drugs is, along with damage to the gastrointestinal tract, kidney damage.

Side effects of drugs (MD) are a serious medical and social problem, which is explained by [19, 24]:

• often unreasonable prescription of drugs, the use of inadequate dosages and unmotivated duration of use;

• interactions between different classes of drugs;

• insufficient understanding of their pharmacodynamic and pharmacokinetic characteristics;

• insufficient knowledge of the characteristics of side effects of drugs of various classes;

• lack of proper monitoring of patients during drug therapy;

• delayed diagnosis of developed side effects, making it difficult to eliminate them and increasing

poor prognosis;

• an increase in the frequency of hospitalizations and deaths caused by side effects of drugs;

• high financial costs for eliminating side effects.

Of course, the largest number of studies are devoted to the development of drug-induced nephropathy with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the use of which is unlikely to be abandoned in the near future. The toxicity of NSAIDs is determined primarily by their selectivity. It has previously been suggested that the cyclooxygenase (COX) isoform regulates the physiological effects of prostaglandins. While an increase in the level of COX type 2 in tissues occurs during inflammatory processes. All this served as the basis for the creation of a new generation of selective NSAIDs (s-NSAIDs), which have all the positive aspects of non-selective NSAIDs (n-NSAIDs), but less toxicity. However, it was later shown that COX2 is constantly synthesized in various parts of the nephron and its metabolites play a significant role in the functioning of both the glomerulus and the tubular apparatus of the kidney [15,13], and the main cause of nephrotoxicity is a decrease in the tissue concentration of prostaglandins, which are synthesized by both isoforms COX [16,14]. Thus, in animal experiments and studies in healthy volunteers, it was revealed that under conditions of reduced sodium intake, COX2 inhibitors increase blood pressure, reduce renal blood flow and glomerular filtration rate (GFR), thereby creating the prerequisites for the development of both acute and chronic nephrotoxicity [22,23].

The kidneys are one of the most commonly affected organs in patients with rheumatological diseases. Kidney damage can be caused either directly by the disease or as a result of complications of the therapy used. Renal manifestations can range from asymptomatic urinary disturbances to serious complications that lead to chronic renal failure [38,3]. However, most rheumatologic diseases complicated by renal disease require immunosuppressive therapy and are associated with higher morbidity and mortality. The nephrologist, along with rheumatologists, plays a key role in the management of such patients, not only in establishing a diagnosis and introducing appropriate treatments in the acute stage of the disease, but also in treating long-term complications such as chronic kidney disease (CKD). On the other hand, patients with CKD may develop rheumatologic symptoms, which must be differentiated from primary rheumatologic disease.

Renal involvement is a direct effect of rheumatologic disease. This is by far the most common cause of kidney damage in rheumatological diseases. The inflammatory process can involve different parts of the kidneys. Some diseases primarily affect the glomerulus

(eg, lupus nephritis), while others affect the small vessels (small vessel vasculitis) or large vessels (Takayasu arteritis) of the kidney, and some diseases primarily affect the interstitium (eg, primary Sjögren's syndrome). Sometimes kidney damage is a consequence of the long-term chronic inflammatory state of these diseases (eg, secondary amyloidosis or accelerated atherosclerosis) [32, 36, 18].

Given the chronicity of these diseases, these patients are often treated with multiple medications over the long term, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologic agents, all of which have the potential to affect the kidneys [4, 21]. .

Non-steroidal anti-inflammatory drugs, due to their excellent anti-inflammatory and analgesic properties, are one of the most commonly used drugs in rheumatological practice. NSAIDs act as cyclooxygenase inhibitors and inhibit prostaglandins E2 and I2, which are potent vasodilators. These drugs have the potential to cause a sharp drop in GFR. They also inhibit the important homeostatic action of prostaglandins on the thick ascending limb of the loop of Henle and the collecting ducts, thereby reducing medullary blood flow and causing apoptosis of medullary interstitial cells [2, 26].

Exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to reversible acute kidney injury or end-stage chronic kidney disease (CKD) due to vasoconstriction, tubular necrosis, and acute interstitial nephritis, regardless of the person's history of kidney disease. Although cumulative lifetime exposure to nonselective NSAIDs has been reported to be associated with decreased renal function, little is known about the evolution of renal function with long-term NSAID therapy. Clinically apparent events are difficult to predict and may occur years later. The gastrointestinal toxicity of NSAIDs can be largely overcome by concomitant use of proton pump inhibitors and the development of cyclooxygenase type 2 selective NSAIDs (coxibs), but nonselective NSAIDs and coxibs carry similar statistical risks of cardiovascular and renal complications as nonselective NSAIDs. According to the definition of contraindications to NSAIDs in current practice guidelines, it is clear that NSAIDs are often used in violation of current safety recommendations [33, 39, 27].

Another option for kidney damage in RA is the development of acute or chronic tubulointerstitial nephritis, in most cases caused by long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics (so-called analgesic nephropathy).

In the development of such nephritis, immunological factors are crucial. In the event of tubulointerstitial nephritis, the drug acts as an antigen. With prolonged use of conventional dosages of drugs, renal dysfunction may occur; with systematic use in large quantities, chronic interstitial nephritis with papillary necrosis may occur. Some disease-modifying anti-inflammatory drugs used to treat RA may cause specific changes in the kidneys [17].

Currently, there are no accurate data on the prevalence of kidney damage in patients with RA. Information is drawn from the analysis of various sources of death certificates,

autopsy data, clinical and laboratory studies, results of puncture biopsy of the kidneys), each of which has its own limitations. The most unfavorable variant of kidney damage in RA, which often determines the course and prognosis of the disease, is secondary amyloidosis [5,40].

Various types of kidney damage in rheumatoid arthritis have been described, in particular, glomerulonephritis, amyloidosis, vasculitis, as well as iatrogenic forms (analgesic tubulopathies, membranous nephropathy, etc.) [35,30].

It is noteworthy that in real clinical conditions, such patients may not undergo morphological verification of renal pathology for a long time for a number of objective reasons. Early manifestations of functional renal disorders, especially when they are moderate, do not always attract the attention of clinicians, while the progression of chronic kidney disease (CKD) in RA can be rapid, especially in old age, as well as when associated with cardiovascular pathology [ 8, 11].

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