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TO'QIMALAR BUZILISHI BIOMARKERLARINING REVMATOID ARTRITDA DAVOLASH VA NATIJA PROGNOZIDA TUTGAN O'RNI (ADABIYOTLAR SHARHI)

Kasparova Gayane Arturovna
Samarqand davlat tibbiyot universiteti, Samarqand, O'zbekiston

Annotatsiya. Revmatoid artrit (RA) — bu biologik preparatlar va JAK ingibitorlari bilan zamonaviy davolashga qaramay, surunkali sinovial yallig'lanish, to'qima buzilishi va suyak eroziyasiga olib keladigan tizimli autoimmun kasallik. An'anaviy baholash usullari (DAS28, tasvirlash) har doim ham strukturaviy o'zgarishlar bilan mos kelmaydi. Hujayradan tashqari matritsaning degradatsiyasi biomarkerlari (COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, CRTAC1) to'qima metabolizmini ob'ektiv monitoring qilish, kasallik progresini bashorat qilish va klinik faollikdan mustaqil ravishda davolash samaradorligini baholash imkonini beradi. 2020–2025 yillardagi tadqiqotlar sharhi ushbu markerlarning bemorlarni stratifikatsiya qilish, davolashni shaxsiy lashtirish va nogironlik xavfini kamaytirish uchun prognozik qiymatini tasdiqlaydi.

Kalit so'zlar: revmatoid artrit, to'qima buzilishi biomarkerlari, COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, bashorat, shaxsiy lashtirilgan terapiya.

РОЛЬ БИОМАРКЕРОВ ХРЯЩЕВОЙ ДЕСТРУКЦИИ В ТЕРАПИИ И ПРОГНОЗИРОВАНИИ ИСХОДОВ ПРИ РЕВМАТОИДНОМ АРТРИТЕ (ОБЗОР ЛИТЕРАТУРЫ)

Каспарова Гаянэ Артуровна
Самаркандский государственный медицинский университет, Самарканд, Узбекистан

Аннотация. Ревматоидный артрит (РА) — это системное аутоиммунное заболевание, приводящее к хроническому воспалению синовиальной оболочки, разрушению хряща и эрозии кости, несмотря на современную терапию биологическими препаратами и ингибиторами JAK. Традиционные методы оценки (DAS28, визуализация) не всегда коррелируют со структурными изменениями. Биомаркеры деградации внеклеточного матрикса (COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, CRTAC1) позволяют объективно мониторить метаболизм хряща, прогнозировать прогрессирование и оценивать эффективность лечения независимо от клинической активности. Обзор исследований 2020–2025 годов подтверждает прогностическую ценность этих маркеров для стратификации пациентов, персонализации лечения и снижения риска инвалидности.

Ключевые слова: ревматоидный артрит, биомаркеры, хрящевая деструкция, COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, прогноз, персонализированная терапия.

THE ROLE OF CARTILAGE DESTRUCTION BIOMARKERS IN THERAPY AND OUTCOME PREDICTION IN RHEUMATOID ARTHRITIS (LITERATURE REVIEW)

Kasparova Gayane Arturovna
Samarkand State Medical University, Samarkand, Uzbekistan

Abstract. Rheumatoid arthritis (RA) is a systemic autoimmune disease leading to chronic synovial inflammation, cartilage destruction, and bone erosion, despite modern therapy with biological agents and JAK inhibitors. Traditional assessment methods (DAS28, imaging) do not always correlate with structural changes. Biomarkers of extracellular matrix degradation (COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, CRTAC1) enable objective monitoring of cartilage metabolism, prediction of progression, and evaluation of treatment efficacy independently of clinical activity. A review of studies from 2020–2025 confirms the prognostic value of these markers for patient stratification, treatment personalization, and reduction of disability risk.

Keywords: rheumatoid arthritis, cartilage destruction biomarkers, COMP, CTX-II, C2M, C1M, C3M, CRPM, VICM, prediction, personalized therapy.

Introduction. Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects synovial joints, leading to inflammation, cartilage destruction, and bone erosion [1-2]. Despite advances in therapy (biological agents, JAK inhibitors), 20–40% of patients continue to experience progression of joint destruction, resulting in disability [3-4]. Traditional assessment methods (DAS28, radiography, MRI) have limitations; for example, clinical remission does not always correlate with the absence of structural damage [5].

Biomarkers of cartilage destruction are fragments of the extracellular matrix (ECM) released during cartilage degradation under the action of matrix metalloproteinases (MMPs) and other enzymes [6-7]. They enable objective real-time assessment of cartilage metabolism, prediction of disease progression, and monitoring of treatment efficacy [8-9].

In the era of personalized medicine, biomarkers help stratify patients by risk of progression, select optimal therapy, and evaluate its impact on structural changes independently of clinical activity [10]. Studies from 2020–2025 confirm the role of classical markers (COMP, CTX-II) and identify new promising ones (C1M, C3M, CRPM, VICM, CRTAC1), particularly in seronegative RA [11-13].

Purpose of the literature review is to systematically analyze the role of cartilage destruction biomarkers in predicting disease outcomes, monitoring therapy efficacy, and personalizing treatment in patients with rheumatoid arthritis, based on recent evidence from 2020–2025, with a focus on their correlation with structural changes and progression.

Materials and Methods. This literature review was conducted by searching electronic databases including PubMed, Scopus, Web of Science, and Google Scholar for articles published between January 1, 2020, and December 31, 2025. The search strategy used keywords and MeSH terms such as "rheumatoid arthritis," "cartilage destruction biomarkers," "COMP," "CTX-II," "C2M," "C1M," "C3M," "CRPM," "VICM," "CRTAC1," "extracellular matrix degradation," "personalized therapy," and "outcome prediction." Boolean operators (AND, OR) were applied to refine searches, and filters were used for English-language publications, human studies, and review/meta-analysis types where applicable.

Inclusion criteria encompassed original research, cohort studies, meta-analyses, and systematic reviews focusing on biomarkers of cartilage destruction in RA, their prognostic value, and association with therapy response. Exclusion criteria included studies on non-RA conditions, animal models only, or publications before 2020 (except for foundational references). A total of 150 articles were initially screened by title and abstract, with 50 full-text articles reviewed for relevance. Data extraction focused on biomarker descriptions, correlations with RA progression, therapy outcomes, and statistical metrics (e.g., odds ratios, AUC values). Qualitative synthesis was

performed without formal meta-analysis due to heterogeneity in study designs. The review also incorporated physiological context and clinical implications from selected studies.

Results. RA is characterized by chronic inflammation of the synovial membrane (synovitis), leading to the formation of pannus—an aggressive hyperplastic tissue that invades and destroys articular cartilage and subchondral bone [14]. Key roles are played by proinflammatory cytokines (TNF-α, IL-6, IL-1), which activate synovial fibroblasts (RA-FLS) and macrophages [15]. RA-FLS acquire a tumor-like phenotype: they proliferate, migrate, and secrete MMPs (MMP-1, MMP-3, MMP-13) that degrade type II collagen—the primary component of the cartilage matrix [16].

Degradation of cartilage ECM results in the release of fragments detected as biomarkers (CTX-II, C2M, COMP, etc.) [17]. Additionally, osteoclasts are activated (via RANKL), causing bone erosions, and synovial fibrosis occurs (C1M, C3M) [18]. Chronic inflammation enhances oxidative stress and macrophage activity (VICM, CRPM), exacerbating destruction [19].

These changes explain why elevated biomarker levels correlate with rapid progression, while their reduction under therapy is associated with slowed destruction [20-21].

Main Biomarkers of Cartilage Destruction.

Classical Biomarkers

COMP (Cartilage Oligomeric Matrix Protein): A non-collagenous protein of cartilage ECM. Elevated serum COMP levels correlate with radiographic progression and RA activity. In studies from 2020–2025, low baseline COMP predicted a good response to adalimumab and tocilizumab [22-23].

CTX-II (C-terminal telopeptide of type II collagen): A marker of MMP-mediated degradation of type II collagen, the main cartilage component. Urinary/serum levels are elevated in active RA and decrease with effective therapy (methotrexate, TNF-α inhibitors) [21]. CTX-II independently predicts long-term progression (OR up to 4.0) [22].

C2M: An MMP-generated fragment of type II collagen. High C2M is associated with inflammation and rapid cartilage destruction in RA [12].

Promising and Understudied Biomarkers.

C1M and C3M (MMP-degraded fragments of type I and III collagen): Reflect degradation of interstitial matrix and synovial fibrosis. In 2020–2025 studies, the combination C1M + C3M + CRPM predicted response to tocilizumab (AUC 0.80–0.85) and progression in early RA [21-23].

CRPM (MMP-degraded C-reactive protein): A marker of chronic inflammation and tissue remodeling. High CRPM correlates with disease activity and progression, complementing classical CRP [13].

VICM (citrullinated and MMP-degraded vimentin): Specific for macrophage activity and autoimmune processes. Promising for seronegative RA and monitoring treatment response [20-22].

CRTAC1 (Cartilage Acidic Protein 1): A novel proteomic marker of cartilage degradation. In 2023–2025 studies, elevated CRTAC1 was associated with RA severity and progression, especially in combination with other markers [23-24].

These markers are understudied in RA but demonstrate high specificity for tissue remodeling [15-16].

Evidence-Based Analysis (2020–2025).

Meta-analyses and cohort studies confirm that elevated baseline COMP, CTX-II, and C2M are independent predictors of progression (OR 2.5–4.5) [17]. Reduction in levels under therapy (tocilizumab, baricitinib) correlates with slowed destruction [18-19].

In phase III trials (LITHE, OSKIRA), combinations of C1M, C2M, C3M, and CRPM predicted structural response with AUC >0.80 [10-11]. New markers (VICM, CRTAC1) improve diagnosis of seronegative RA and patient stratification [12].

Systematic Reviews and Meta-Analyses.

In the review by Bay-Jensen et al. (2022–2025), extracellular matrix remodeling markers (C1M, C2M, C3M, CRPM) were examined. Combinations of these markers (e.g., C1M + C2M + CRPM) predicted structural progression and response to tocilizumab with AUC 0.80–0.85. The markers reflect tissue destruction and are useful for therapy monitoring in RA [23].

In the systematic review by Groen et al. (2025), serum biomarkers (C1M, C2M, C3M, PRO-C3, PRO-C6, VICM) were evaluated in patients with RA, psoriatic arthritis, and psoriasis. Levels were elevated compared to controls and correlated with impaired hand function. VICM and CRPM are specific for inflammation and macrophage activity in RA [11].

In the meta-analysis by Thudium et al. (2020–2023), the effect of baricitinib on joint destruction biomarkers (CTX-II, COMP, C2M) was studied. Reduction in levels correlated with slowed progression. Combined panels improved the accuracy of predicting structural changes [8].

In the review by Wang et al. (2025) using machine learning, plasma metabolites and biomarkers (including CTX-II and COMP) were analyzed for early prediction of bone destruction in RA. Biomarker-based models achieved high accuracy in identifying rapidly progressive forms [12].

Advantages of Using Biomarkers.

1. Early detection of progressive forms (before radiographic changes).
2. Assessment of treatment efficacy independently of DAS28 (structural response).
3. Personalization: selection of biological agents or JAK inhibitors.
4. Reduction in radiation exposure and costs associated with frequent imaging.

Strategies for Integration into Clinical Practice.

It is recommended to measure a panel (COMP + CTX-II + C2M + C1M/C3M) at baseline and after 3–6 months. A reduction >30–40% indicates a favorable response. An interdisciplinary approach involving rheumatologists and laboratory specialists is advised.

Limitations and Future Perspectives.

Variability in levels, influence of comorbidities, need for standardization. Future perspectives: integration with genetics, validation of new markers (CRTAC1, VICM) in large cohorts.

Conclusion. Biomarkers of cartilage destruction (both classical and novel) play a key role in predicting and monitoring RA. Their use enables a shift toward personalized therapy, reducing the risk of disability. Further research is needed for standardization and routine clinical implementation.

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