Letter to the Editor / Editöre Mektup

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Turk J Osteoporos

Cell-free DNA and Fragmentomics as Biomarkers of Rheumatoid Arthritis Disease

Romatoid Artrit Hastalığında Biyobelirteç Olarak Hücre Dışı DNA ve Fragmentomik Yaklaşımlar

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Dear Editor,

We read with great interest the article entitled "Can the Systemic Immune-Inflammation Index Reflect Disease Activity in Patients with Rheumatoid Arthritis?" published in the Turkish Journal of Osteoporosis. The authors addressed a clinically relevant and timely question and provided valuable data supporting the potential utility of the systemic immune-inflammation index (SII) as an easily accessible biomarker for assessing disease activity in patients with rheumatoid arthritis (RA) (1).

RA remains a paradigmatic example of a chronic systemic inflammatory disease in which accurate, dynamic, and biologically meaningful assessment of disease activity is central to patient management. In this regard, composite indices such as disease activity score-28, acute-phase reactants, and hematologic inflammation-derived markers, including SII—calculated from neutrophil, lymphocyte, and platelet counts—are widely used. The appeal of SII lies in its simplicity, low cost, and broad availability, making it particularly attractive in daily clinical settings. The present study reinforces the relevance of SII as part of this pragmatic assessment framework (2).

Building upon the authors' important observations, we would like to draw attention to circulating cell-free DNA (cfDNA) as a promising complementary biomarker that may further enrich the evaluation of disease activity in RA. Hematologic indices such as SII reflect systemic inflammatory responses and are influenced by multiple physiological and clinical factors, including infections, stress responses, medications, and comorbid conditions—factors that are commonly encountered in RA populations. In this context, cfDNA offers an additional, molecular-level perspective by reflecting ongoing cell death and tissue turnover associated with inflammatory processes (3).

Beyond total cfDNA concentration, cfDNA fragmentomics—encompassing fragment size distribution, end motifs, nucleosomal patterns, and genomic origin—provides an additional layer of biologically informative data. Fragmentation profiles may reflect dominant cell death mechanisms such as apoptosis or NETosis, both of which are central to RA pathogenesis. Moreover, fragmentomic signatures may offer insights into the cellular and tissue sources of inflammation, information that cannot be derived from conventional blood count-based indices alone (4).

Importantly, cfDNA-based approaches may also support longitudinal and non-invasive monitoring with high temporal resolution. Changes in cfDNA levels or fragmentomic patterns could potentially precede clinical flares or alterations in conventional inflammatory markers, allowing earlier therapeutic adjustments. In this sense, cfDNA analysis aligns well with emerging precision medicine strategies and may be integrated with other molecular and clinical parameters to enhance individualized disease management (3,4).

We acknowledge that challenges remain before cfDNA and fragmentomics can be routinely implemented in rheumatology practice, including standardization of pre-analytical procedures, analytical pipelines, and reference ranges. Cost and technical

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requirements currently exceed those of readily available indices such as SII. However, given the rapid technological advances and expanding clinical use of cfDNA in other fields, these limitations are likely to diminish over time.

In conclusion, the authors' study provides valuable evidence supporting the clinical relevance of SII in RA. We suggest that cfDNA profiling and cfDNA fragmentomics may serve as complementary, pathophysiology-oriented tools that build upon and extend the utility of inflammation-based indices such as SII. Future prospective studies comparing SII, cfDNA- based metrics, clinical scores, imaging findings, and treatment outcomes may help to further refine and optimize disease activity monitoring in RA.

Sincerely,

Footnotes

Authorship Contributions

Design: H.G.D., A.A., Analysis or Interpretation: H.G.D., A.A., Literature Search: H.G.D., A.A., Writing: H.G.D., A.A.

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