مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
العدد السادس والعشرون - المجلد السادس - علوم الكيمياء - كانون أول 2025 م
doi.org/10.52866/esj.2025.06.26.23

The role of biochemical markers in the diagnosis and pathogenesis of rheumatoid arthritis

Ali Hussein Abdulghafoor[1] , Firas shawqi Algburi[2]
[1] Kirkuk Health Directorate, Ministry of Health
[2] Department of chemistry/college of science/Tikrit University
E1: Ah240027me@st.tu.edu.iq E2: dr.firas.shawki@tu.edu.iq

Abstract:

The present study included 90 samples: 70 patients with rheumatoid arthritis (RA) and 20 healthy controls. The study was conducted from January 2025 to May 2025. Patients with rheumatoid arthritis were selected from Kirkuk General Hospital and Azadi Teaching Hospital. Patients were evaluated clinically, and laboratory investigations were carried out following WHO recommendations. Concentrations of serum Annexin A1, Ficolin-1, Nidogen-1, and Nesprin-2 were assayed by ELISA kits. The findings demonstrated significant differences in the concentrations of serum Annexin A1, Ficolin-1, Nidogen-1, and Nesprin-2 levels between the RA group and the control group. The levels of Nesprin-2, Ficolin-1, and Nidogen-1 were also found to be up-regulated in patients with RA, suggesting their involvement in immune response and tissue remodeling. By contrast, levels of Annexin A1 also underwent a statistically significant reduction. The results indicated that these biomarkers may serve as valuable indicators for the diagnosis of RA and for investigating its pathogenesis.

Keyword: Biochemical Markers, Diagnosis, Pathogenesis, Annexin A1, Rheumatoid Arthritis.

دور المؤشرات الكيميائية الحيوية الجديدة في تشخيص والتسبب بمرض التهاب المفاصل الروماتويدي

علي حسين عبد الغفور ، فراس شوقي الجبوري
دائرة صحة كركوك، وزارة الصحة قسم الكيمياء، كلية العلوم، جامعة تكريت

مستخلص:

شملت الدراسة الحالية 90 عينة، منها 70 عينة لمرضى مصابين بالتهاب المفاصل الروماتويدي و20 عينة لأشخاص أصحاء كمجموعة ضابطة. وقد أُجريت الدراسة خلال الفترة من يناير إلى مايو 2025، حيث تم اختيار المرضى من مستشفى كركوك العام ومستشفى آزادي التعليمي. خضع المرضى لتقييم سريري، وتم إجراء الفحوصات المختبرية وفقاً لتوصيات منظمة الصحة العالمية. تم قياس تراكيز كل من Annexin A1 و Ficolin-1 و Nidogen-1 و Nesprin-2 في مصل الدم بطريقة ELISA . أظهرت النتائج وجود فروقات معنوية في مستويات المؤشرات الحيوية بين مجموعة مرضى التهاب المفاصل الروماتويدي والمجموعة الضابطة. كما لوحظ ارتفاع في التعبير الجيني لكل من Nesprin-2 و Ficolin-1 و Nidogen-1 لدى مرضى التهاب المفاصل الروماتويدي، مما يشير إلى دورها المحتمل في الاستجابة المناعية وإعادة تشكيل الأنسجة. في المقابل، أظهرت مستويات Annexin A1 انخفاضاً معنوياً من الناحية الإحصائية.

وأشارت النتائج إلى أن هذه المؤشرات الحيوية قد تكون بمثابة مؤشرات قيمة لتشخيص التهاب المفاصل الروماتويدي والتحقيق في مسبباته.

الكلمات المفتاحية: مؤشرات حيوية، التشخيص، الآليات المرضية، التهاب المفاصل الروماتويدي.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that affects approximately 1% of the world's population. Its development is influenced by a combination of genetic and environmental factors, and can be further impacted by lifestyle changes such as smoking and dietary habits [1,2]. RA is characterized by persistent synovitis, systemic inflammation, and progressive cartilage and bone destruction, ultimately leading to joint deformity [3]. The course of the disease is unpredictable, with intermittent flares over time; however, without effective treatment, symptoms generally worsen, resulting in permanent joint damage and deterioration in both physical and psychological functioning [4]. Evidence suggests that the pathogenesis of RA may begin at mucosal sites before reaching the synovium [5].

These biomarkers were selected based on their potential involvement in key pathological mechanisms of rheumatoid arthritis. Nesprin-2, through its role in cytoskeletal organization and nuclear positioning, may influence synovial cell function and joint tissue integrity, which are often disrupted in RA [6]. Ficolins, as activators of the lectin complement pathway, are implicated in immune-mediated inflammation and could reflect disease activity [7]. Annexin A1, a potent anti-inflammatory mediator regulated by glucocorticoids, may serve as an indicator of both inflammation status and treatment response [8]. Nidogen-1, a critical component of the extracellular matrix, is essential for maintaining joint structural stability, and its alterations may contribute to cartilage and bone destruction [9]. Evaluating these parameters together could provide a more comprehensive understanding of RA pathogenesis and improve diagnostic precision.

Nesprin-2 is a type II transmembrane protein located in the outer nuclear membrane (ONM) and plays a crucial role in linking the nucleus to the cytoskeleton. It functions partially redundantly with Nesprin-1 and, in addition to associating with microtubules, it also binds to the actin cytoskeleton. This interaction helps maintain nuclear shape, position, and signal transduc-

tion. Mutations in Nesprin-2 have been associated with muscular dystrophy, cardiomyopathy, and progeria [10]. In the context of RA, alterations in cytoskeletal organization and nuclear positioning—processes in which Nesprin-2 is critically involved—may contribute to synovial cell dysfunction and joint tissue damage [11].

Ficolins are a group of proteins, originated as a binding protein of transforming growth factor (TGF)-b1, that were first reported in swine uterine membranes in 1993 [12]. Ficolins have been shown as enhancers in the activation of the lectin complement pathway of the complement system and defenders of the host against infection of pathogens. Ficolins are identified as innate soluble pattern recognition molecules PRMs, which are complexed with mannose-binding lectin-associated serine proteases (MASPs) [13].

Annexin A1 (ANXA1) is a glucocorticoid-regulated protein that plays a key role in resolving inflammation by inhibiting leukocyte migration and promoting anti-inflammatory signaling [14]. In RA, reduced levels or impaired function of ANXA1 may contribute to persistent synovial inflammation and joint damage [15]. Annexin A2 (ANXA2), on the other hand, is involved in angiogenesis, fibrinolysis, and extracellular matrix degradation [16]. In RA, ANXA2 has been implicated in pannus formation and synovial tissue invasion into cartilage and bone. While both belong to the annexin family and participate in inflammation, ANXA1 primarily acts as an anti-inflammatory mediator, whereas ANXA2 is associated with pro-inflammatory and tissue-invasive processes in RA [17].

Nidogen-1 (entactin) is a glycoprotein that is involved in the structural assembly of the extracellular matrix (ECM) [18]. The protein Nidogen-1 plays a vital role in preserving the tissue's homeostasis and dynamics by connecting various extracellular matrix molecules (ECM), which in turn influences their molecular and mechanical characteristics [19].

The objective of this study is to analyze the diagnostic value of clinical and biochemical parameters of RA. It studies if ficolins are mediators of disease activity, nesprin-1 of muscle

involvement, annexin A1 of inflammation and glucocorticoid response, and nidogen-1 of extracellular matrix alterations and joint destruction.

Materials and methods

Study Population: The study included ninety participants, comprising 30 male and 40 female RA patients and 10 male and 10 female healthy individuals as the control group. All participants were sex- and age-matched, aged between 30 and 70 years. They attended Kirkuk General Hospital and Azadi Teaching Hospital during the period from January to May 2025. Relevant demographic, medical, and lifestyle information were obtained through a structured questionnaire. The diagnosis of RA was established according to the most recent WHO clinical practice guidelines and classification criteria. All patients underwent thorough medical history taking, physical examination, and appropriate laboratory investigations. The control group consisted of healthy volunteers with no history or clinical signs of rheumatoid arthritis. The study protocol was reviewed and approved by the Ethics Committee of Kirkuk Health Directorate, and written informed consent was obtained from all participants prior to enrolment.

Serum collection and analysis:

Serum samples were analyzed for Annexin A1, Ficolin-1, Nidogen-1, and Nesprin-2 using commercially available sandwich ELISA kits according to the manufacturer's protocols. ELISA assay kits for Annexin A1, Ficolin-1, Nidogen-1, and Nesprin-2 were purchased from Bioassay Technology Laboratory, Jiaxing, Zhejiang, China. Plates were read on a BioTek ELx800 microplate reader (BioTek Instruments, USA) set at 450 nm. Each sample was performed in duplicate to reduce experimental errors.

Statistical Analysis

All data were analyzed using SPSS Statistics software version 20. Descriptive statistics, including mean and standard deviation, were calculated. One-way analysis of variance (ANOVA) was used to compare means between groups. When significant differences were detected, the Duncan multiple range test was applied for post hoc comparisons. A p-value of less than 0.05 ($p < 0.05$) was considered statisti-

cally significant.

Results and Discussion

Serum level of Nesprin-2, Annexin A1, Ficolin-1, and Nidogen-1 in RA Patients Compared to Healthy Controls

The results presented in Table (1) reveal statistically significant differences in the level of immunological and structural biomarkers between rheumatoid arthritis (RA) patients and healthy controls ($P < 0.001$ for all variables). The raised level of Nesprin-2 in RA patients, a nuclear envelope protein involved in cellular organization and immune response regulation [20], suggested its role in pathological remodeling mechanisms of the disease. Annexin A1 was diminished in the RA patients versus controls, while being a well-recognized anti-inflammatory factor. This decrease is consistent with the theory of an impaired endogenous anti-inflammatory process in RA that results in continued inflammation [21].

Moreover, Ficolin1, which is responsible for activating the lectin pathway of complement, was significantly elevated in RA patients as evidence of increased innate immune activity [22]. In the same line, the presence of Nidogen1 a basement membrane glycoprotein involved into the tissue structure and repair process also evidenced higher immunoreactivity in patients [23], consistent with possible synovial tissue remodeling or destruction. These results together indicate the diagnosis and the pathogenesis significance of these biomarkers for RA. Their unique expression profiles and differences between patients and controls reflect not only their diagnostic value, but also pathogenic significance of immune and tissue-related changes in the development of RA.

Table (1) Comparison of Serum Levels of Biomarkers Between RA Patients and Healthy Controls

Group	Patient No. (70) mean ± SD	Controls No. (20) mean ± SD	P-value
Nesprin-2	1580 ± 283	1456 ± 240	0.001
Annexin A1	7.190 ± 1.15	9.876 ± 0.931	0.0005
Ficolin - 1	80.45 ± 7.57	51.32 ± 9.99	0.0006
Nidogen - 1	5.97 ± 1.14	2.91 ± 1.13	0.0005

P<0.05 is considered to be significantly different

Nesprin-2 levels were significantly elevated in RA patients (1580 ± 283 ng/mL) compared to controls (1456 ± 240 ng/mL, P = 0.001). Nesprin-2 is a nuclear envelope protein involved in cytoskeletal anchoring. This finding is consistent with the study by Xiao *et al* 2021 [24], which reported abnormal expression of Nesprins in autoimmune diseases, suggesting their involvement in nuclear architecture disruption in RA pathogenesis.

The current study revealed a significant reduction in Annexin A1 levels in RA patients compared to healthy controls (7.190 ± 1.15 ng/mL vs. 9.876 ± 0.931 ng/mL; P = 0.0005). This finding aligns closely with the results reported by Lee et al. [16], who investigated the reciprocal regulation of Annexin A1 and Annexin A2 in rheumatoid arthritis. In that study, naïve RA patients—meaning patients who have not yet received treatment—exhibited significantly lower levels of Annexin A1 compared to healthy individuals, while Annexin A2 levels were significantly elevated [16]. In both studies, the significant downregulation of Annexin A1 in active RA cases reflects ongoing systemic inflammation and impaired resolution pathways. Thus, our data strongly support the role of Annexin A1 as a sensitive inflammation marker and align with emerging evidence on its diagnostic and therapeutic relevance in RA pathogenesis [16]. The significantly lower levels of Annexin A1 (AnxA1)

observed in our RA patient group, as compared to healthy controls, may reflect a dysregulated endogenous anti-inflammatory response [25]. AnxA1 is now recognized as a pivotal homeostatic and anti-inflammatory mediator, widely distributed in leukocytes, stromal cells, and synovial tissues [26]. It plays a central role in modulating immune responses by inhibiting leukocyte recruitment, suppressing pro-inflammatory cytokines (e.g., TNF-α, PGE2, NO), and promoting apoptosis of inflammatory cells [27].

Our findings align with previous studies indicating that deficiency of AnxA1 exacerbates inflammation in RA animal models and reduces the effectiveness of glucocorticoid therapy [28]. Since glucocorticoids upregulate AnxA1 synthesis and translocation, the low serum AnxA1 levels detected in our RA cohort may suggest either insufficient endogenous anti-inflammatory control or impaired glucocorticoid signaling [29]. This supports the hypothesis that impaired AnxA1 expression or function could contribute to persistent synovial inflammation and joint destruction in RA. Furthermore, the regulatory relationship between AnxA1 and glucocorticoids suggests its potential as both a biomarker for disease activity and a target for novel anti-inflammatory therapies [30]. The glucocorticoid-mimetic action of the bioactive N-terminal acetylated peptide Ac2-26, of AnxA1, could be a therapeutic approach for modulating inflammation in RA [31].

The levels of ficolin-1 were significantly higher in RA patients than in controls (80.45 ± 7.57 vs 51.32 ± 9.99 ng/mL, P = 0.0006). Katayama et al. [32] found that the levels of serum FCN1 were not only increased in RA but also in other autoimmune diseases, including vasculitis and Kawasaki disease. In addition, therapeutic administrations of anti-FCN1 antibody significantly attenuated the symptom of arthritis in a mouse model, indicating that FCN1 might have a potential as a biomarker as well as a target of therapeutic intervention [33]. These results are consistent with our data, and it again underlines the potential of Ficolin-1 as a relevant tool in the diagnosis and treatment of autoimmune diseases as RA [34].

Findings from C. Pieczarka *et al*. research are consistent with our results and further confirm the implication of Ficolin-1 (FCN1) in the development of RA [35]. The latter work summarizes a genetic view that certain polymorphisms of the FCN1 locus like the rs10120023 (g.-542G>A) polymorphism are associated with an enhanced risk for RA that is associated with a differential expression. Specific haplotypes such as AAGAG were also found to be more frequent in RF seronegative patients indicative that genetics may influence both the risk of disease and its pattern of presentation. This study, accompanied with their genetic evidence and our biochemical data of increased FCN1 levels, supports the idea of the involvement of Ficolin-1 in the development of RA and that it might be useful as a biomarker and a target for personalized medicine according to the patient's genetic profile.Nidogen-1 was also found to be significantly elevated in RA patients (5.97 ± 1.14 ng/mL) compared to controls (2.91 ± 1.13 ng/mL, P = 0.0005). The significantly higher levels of Nidogen-1 in RA patients compared to controls suggest that Nidogen-1 may play a role in the pathological changes of the extracellular matrix associated with rheumatoid arthritis [36]. This glycoprotein is involved in maintaining the structural integrity of tissues, and its increased levels could reflect active tissue remodeling or joint destruction in RA. Therefore, Nidogen-1 might serve as a potential biomarker for disease activity and progression in RA patients [37].

This study concludes that the biomarkers Nesprin-2, Ficolin-1, and Nidogen-1 are significantly upregulated in patients with rheumatoid arthritis (RA), indicating their potential involvement in immune response and tissue remodeling processes associated with the disease. Conversely, Annexin A1 levels are notably decreased in RA patients. These findings suggest that these biomarkers could serve as valuable tools for diagnosing RA and advancing the understanding of its underlying pathogenesis.

References

[1] C. Gioia, B. Lucchino, M. G. Tarsitano, C. Iannuccelli, and M. Di Franco, "Dietary habits and nutrition in rheumatoid arthritis: can diet influence disease development and clinical manifestations?," *Nutrients*, vol. 12, no. 5, p. 1456, 2020.

[2] B. Lucchino, F. R. Spinelli, C. Iannuccelli, M. P. Guzzo, F. Conti, and M. Di Franco, "Mucosa–Environment interactions in the pathogenesis of rheumatoid arthritis," *Cells*, vol. 8, no. 7, p. 700, 2019.

[3] K. Okamoto and H. Takayanagi, "Osteoimmunology," *Genet. Bone Biol. Skelet. Dis.*, pp. 261–282, 2018.

[4] N. Chaurasia, A. Singh, I. L. Singh, T. Singh, and T. Tiwari, "Cognitive dysfunction in patients of rheumatoid arthritis," *J. Fam. Med. Prim. Care*, vol. 9, no. 5, pp. 2219–2225, 2020.

[5] V. M. Holers *et al.*, "Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction," *Nat. Rev. Rheumatol.*, vol. 14, no. 9, pp. 542–557, 2018.

[6] Zi-Yi, Z., Qin, Q., Fei, Z., Cun-Yu, C., & Lin, T. (2024). Nesprin proteins: bridging nuclear envelope dynamics to muscular dysfunction. *Cell Communication and Signaling*, *22*(1), 208.

[7] Catarino, S. J., Andrade, F. A., Boldt, A. B. W., Guilherme, L., & Messias-Reason, I. J. (2018). Sickening or healing the heart? The association of ficolin-1 and rheumatic fever. *Frontiers in immunology*, *9*, 3009.

[8] Haridas, V., Shetty, P., Sarathkumar, E., Bargale, A., Vishwanatha, J. K., Patil, V., & Dinesh, U. S. (2019). Reciprocal regulation of pro-inflammatory Annexin A2 and anti-inflammatory Annexin A1 in the pathogenesis of rheumatoid arthritis. Molecular Biology Reports, 46(1), 83-95.

[9] Flood, S. L., Duance, V. C., & Mason, D. J. (2004). The role of glutamate signalling in rheumatoid arthritis. International Journal of Experimental Pathology, 85(1), A19-A20.

[10] A. Janin and V. Gache, "Nesprins and lamins in health and diseases of cardiac and skeletal muscles," *Front. Physiol.*, vol. 9, p. 1277, 2018.

[11] Casciaro, F. (2019). Role of nuclear redox control, intra-population

heterogeneity and oxygen tension in human amniotic fluid stem cells aging.

[12] H. Ichijo *et al.*, "Molecular cloning and characterization of ficolin, a multimeric protein with fibrinogen-and collagen-like domains," *J. Biol. Chem.*, vol. 268, no. 19, pp. 14505–14513, 1993.

[13] S. Bidula, D. W. Sexton, and S. Schelenz, "Ficolins and the recognition of pathogenic microorganisms: an overview of the innate immune response and contribution of single nucleotide polymorphisms," *J. Immunol. Res.*, vol. 2019, no. 1, p. 3205072, 2019.

[14] Perretti, M., & D'acquisto, F. (2009). Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. Nature Reviews Immunology, 9(1), 62-70.

[15] Haridas, V., Shetty, P., Sarathkumar, E., Bargale, A., Vishwanatha, J. K., Patil, V., & Dinesh, U. S. (2019). Reciprocal regulation of pro-inflammatory Annexin A2 and anti-inflammatory Annexin A1 in the pathogenesis of rheumatoid arthritis. Molecular Biology Reports, 46(1), 83-95.

[16] Haridas, V., Shetty, P., Sarathkumar, E., Bargale, A., Vishwanatha, J. K., Patil, V., & Dinesh, U. S. (2019). Reciprocal regulation of pro-inflammatory Annexin A2 and anti-inflammatory Annexin A1 in the pathogenesis of rheumatoid arthritis. *Molecular Biology Reports*, *46*(1), 83-95.

[17] In RA, ANXA2 has been implicated in pannus formation and synovial tissue invasion into cartilage and bone. While both belong to the annexin family and participate in inflammation, ANXA1 primarily acts as an anti-inflammatory mediator, whereas ANXA2 is associated with pro-inflammatory and tissue-invasive processes in RA.

[18] J.-L. Zhang *et al.*, "Vertebrate extracellular matrix protein hemicentin-1 interacts physically and genetically with basement membrane protein nidogen-2," *Matrix Biol.*, vol. 112, pp. 132–154, 2022.

[19] U. Töpfer, K. Y. Guerra Santillán, E. Fischer-Friedrich, and C. Dahmann, "Distinct contributions of ECM proteins to basement membrane mechanical properties in Drosophila," *Development*, vol. 149, no. 10, p. dev200456, 2022.

[20] Zi-Yi, Z., Qin, Q., Fei, Z., Cun-Yu, C., & Lin, T. (2024). Nesprin proteins: bridging nuclear envelope dynamics to muscular dysfunction. Cell Communication and Signaling, 22(1), 208.

[21] Kelly, L., McGrath, S., Rodgers, L., McCall, K., Tulunay Virlan, A., Dempsey, F., ... & Goodyear, C. S. (2022). Annexin-A1: the culprit or the solution?. Immunology, 166(1), 2-16.

[22] Hein, E., Nielsen, L. A., Nielsen, C. T., Munthe-Fog, L., Skjoedt, M. O., Jacobsen, S., & Garred, P. (2015). Ficolins and the lectin pathway of complement in patients with systemic lupus erythematosus. Molecular immunology, 63(2), 209-214.

[23] Mortensen, J. H., Lindholm, M., Langholm, L. L., Kjeldsen, J., Bay-Jensen, A. C., Karsdal, M. A., & Manon-Jensen, T. (2019). The intestinal tissue homeostasis–the role of extracellular matrix remodeling in inflammatory bowel disease. Expert review of gastroenterology & hepatology, 13(10), 977-993.

[24] Z. X. Xiao, J. S. Miller, and S. G. Zheng, "An updated advance of autoantibodies in autoimmune diseases," *Autoimmun. Rev.*, vol. 20, no. 2, p. 102743, 2021.

[25] A. M. Kamal, R. J. Flower, and M. Perretti, "An overview of the effects of annexin 1 on cells involved in the inflammatory process," *Mem. Inst. Oswaldo Cruz*, vol. 100, pp. 39–48, 2005.

[26] Haridas, V., Shetty, P., Sarathkumar, E., Bargale, A., Vishwanatha, J. K., Patil, V., & Dinesh, U. S. (2019). Reciprocal regulation of pro-inflammatory Annexin A2 and anti-inflammatory Annexin A1 in the pathogenesis of rheumatoid arthritis. Molecular Biology Reports, 46(1), 83-95.

[27] H. B. Patel *et al.*, "The impact of endogenous annexin A1 on glucocorticoid control of inflammatory arthritis," *Ann. Rheum. Dis.*, vol. 71, no. 11, pp. 1872–1880, 2012.

[28] Patel, H. B., Kornerup, K. N., Andre'LF, S., D'Acquisto, F., Seed, M. P., Girol, A. P., ... & Perretti, M. (2012). The impact of endogenous annexin A1 on glucocorticoid control of inflammatory arthritis. Annals of the rheumatic diseases, 71(11), 1872-1880.

[29] A. P. Girol *et al.*, "Anti-inflammatory mechanisms of the annex-

in A1 protein and its mimetic peptide Ac2-26 in models of ocular inflammation in vivo and in vitro," *J. Immunol.*, vol. 190, no. 11, pp. 5689–5701, 2013.

[30] A. V Sampey, P. Hutchinson, and E. F. Morand, "Annexin I and dexamethasone effects on phospholipase and cyclooxygenase activity in human synoviocytes," *Mediators Inflamm.*, vol. 9, no. 3–4, pp. 125–132, 2000.

[31] Y. Li *et al.*, "Glycoproteomic analysis of tissues from patients with colon cancer using lectin microarrays and nanoLC-MS/MS," *Mol. Biosyst.*, vol. 9, no. 7, pp. 1877–1887, 2013.

[32] M. Katayama *et al.*, "Ficolin-1 is a promising therapeutic target for autoimmune diseases," *Int. Immunol.*, vol. 31, no. 1, pp. 23–32, 2019.

[33] Katayama, M., Ota, K., Nagi-Miura, N., Ohno, N., Yabuta, N., Nojima, H., ... & Hirano, T. (2019). Ficolin-1 is a promising therapeutic target for autoimmune diseases. International Immunology, 31(1), 23-32.

[34] M. Katayama *et al.*, "Ficolin-1 is a promising therapeutic target for autoimmune diseases," *Int. Immunol.*, vol. 31, no. 1, pp. 23–32, 2019.

[35] C. Pieczarka *et al.*, "Ficolin-1 and ficolin-3 polymorphisms and susceptibility to rheumatoid arthritis," *Autoimmunity*, vol. 53, no. 7, pp. 400–407, 2020.

[36] Kruegel, J., Sadowski, B., & Miosge, N. (2008). Nidogen-1 and nidogen-2 in healthy human cartilage and in late-stage osteoarthritis cartilage. Arthritis & Rheumatism, 58(5), 1422-1432.

[37] Mortensen, J. H., Lindholm, M., Langholm, L. L., Kjeldsen, J., Bay-Jensen, A. C., Karsdal, M. A., & Manon-Jensen, T. (2019). The intestinal tissue homeostasis–the role of extracellular matrix remodeling in inflammatory bowel disease. Expert review of gastroenterology & hepatology, 13(10), 977-993.