https://doi.org/10.70882/c548tp27

SCIENCE FORUM (JOURNAL OF PURE AND APPLIED SCIENCES) 26, (5 Special) (2026), 145 - 158

Science Forum (Journal of Pure and Applied Sciences)

Journal Homepage: https://atbuscienceforum.com.ng/index.php/jpas

Microvascular and Structural Remodeling of the Extracellular Matrix in Autoimmune Organ Damage: A Histopathological and Biomarker Perspective; Article Review

Rusul Faris Kadhim

Department of Pathological Analysis, College of Science, University of Wasit, Wasit, Iraq

Abstract

In the study of autoimmune diseases, interactions among immune dysregulation, microvascular dysfunction and extracellular matrix (ECM) remodeling can result in damage to the organs. Changes in production, organization, cross linking and degradation of matrix proteins can be caused by endothelial injury, alteration in vascular flow, recruitment of inflammatory cells, and continued activation of stromal cells. These changes can lead to tissue stiffness, basement-membrane abnormalities, capillary rarefaction and fibrosis. This narrative review brings together evidence regarding these mechanisms in systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and in particular lupus nephritis (LN) and rheumatoid arthritis (RA), as well as associations between histopathological findings and biomarkers of interest. Classes of biomarkers that are being studied include proteins associated with collagen turnover, matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), transforming growth factor beta (TGF-β) related markers, endothelial-activation markers, angiogenic factors, urinary inflammatory proteins, and urinary renal-injury proteins. The evidence available suggests that the ECMi biomarkers reviewed may be used in conjunction with the clinical and histological evaluation; however, the majority of these are investigational or context-specific. These factors cause disease heterogeneity, assay variation, and systemic sources of analytes and challenges with differentiating active inflammation from established disease structure, complicating interpretation. When tissue level classification is needed, histopathology will continue to be important, and may be supplemented by vascular assessment and biomarker panels, which can give additional information regarding biological activity and its changes over time. For clinical translation, a standardized assay is necessary, a longitudinal cohort, prespecified histological endpoints, external validation, and added value existing beyond the conventional clinical endpoints.

Keywords

Extracellular Matrix;
Microvascular Remodeling;
Autoimmune Disease;
Endothelial Dysfunction;
Histopathology;
Fibrosis;
Collagen Turnover;
Biomarkers;
Systemic Sclerosis;
Lupus Nephritis;
Rheumatoid Arthritis.

EISSN: 3156-5190 (Online)
ISSN: 1119-4618 (Print)
JPAS
Faculty of Science, ATBU Bauchi

Corresponding Author: Rusul Faris Kadhim, Department of Pathological Analysis, College of Science, University of Wasit, Wasit, Iraq.
Email: Rusul.faris@uowasit.edu.iq © 2026 Faculty of Science, ATBU Bauchi. All rights reserved

1. Introduction

Autoimmune diseases involve immune dysregulation and the presence of autoantibodies, autoreactive lymphocytes, cytokines and immune mediated inflammation. Other resident cells produce and maintain the extracellular matrix which also influences organ function, and the microvasculature. The ECM does not just serve as an inert scaffold; it controls cell adhesion, migration, survival, differentiation, mechanical signaling and growth factor availability. Thus its composition and architecture can play a role in tissue homeostasis and the development of chronic diseases [1-6].

Chronic immunoinflammatory processes could damage endothelial cells, modify vascular permeability, reduce vascular perfusion and stimulate the activation of the fibroblasts or other mesenchymal cell populations. Repeated damage and re-repair in susceptible tissues leads to excessive matrix deposition or abnormally matrix degradation. These mechanisms are more evident in systemic sclerosis (SSc) where there is co-existence of vasculopathy and fibrosis and in lupus nephritis (LN) where glomerular inflammation may co-exist with chronic glomerular and tubulointerstitial scarring. [7–17]

One of the most important clinical issues is to differentiate between inflammation, active tissue remodeling and irreversible structural damage. These processes are tied together and not mutually exclusive. A marker of inflammation that circulates in the blood can be a sign of inflammation in other parts of the body but not indicate which organ is involved. Similarly, the change in a matrix-turnover marker does not necessarily reflect a change in the net collagen accumulation. Histopathology can show both acute and chronic lesions, but a biopsy is a snapshot of a specific area, at a specific time and could fail to reflect the distribution or progression of the disease process. The use of microvascular pathology, ECM remodeling, histopathology or biomarkers is therefore not considered as an interchangeable source of evidence for this review.

1.1 Aim and review questions

The purposes of the review were to (i) describe the linkages between immune-mediated endothelial damage and matrix remodeling; (ii) provide a summary of the histopathological features of selected autoimmune diseases; (iii) critically discuss candidate vascular injury, inflammation and ECM turnover biomarkers; and (iv) indicate areas of priority for clinical validation. This article is a narrative review, rather than a systematic review or meta-analysis.

2. Review approach and scope

The literature search for this narrative synthesis is based on published reviews, clinical biomarker studies and literature focused on systemic sclerosis (SSc), lupus nephritis (LN), renal fibrosis, and rheumatoid arthritis (RA). Literature was systematically searched on PubMed using relevant keywords to look for publications on biological mechanisms, tissue findings and the link between the biomarkers and clinical or histological result. No systematic screening of the literature was performed, but rather the literature was chosen because of its relevance to the questions to be answered in the review. The last update of the search was made on 23 October 2026. Original data from patients or laboratories are not reported; results of the clinical trials are summarized qualitatively; no averaging of results is reported.

3. Biological basis of microvascular injury and ECM remodeling

3.1. Endothelial dysfunction and vascular injury

The endothelial cells play a role in vascular tone, barrier function, hemostasis, leukocyte trafficking and angiogenic responses. These functions can be disrupted by cytokines, immune complexes, activation of complement, autoantibodies, oxidative stress and local tissue-derived signals, which are mediated by autoimmune inflammation. This results in a phenotype with increased permeability, expression of adhesion molecules, activation or apoptosis of endothelial cells,

changes in the regulation of vasomotor mechanisms, and a prothrombotic surface. Microscopic damage to the small blood vessels of the skin (microvascular abnormalities) in SSc can be seen clinically by nailfold videocapillaroscopy (NV) which shows enlarged capillaries, microhemorrhages, capillary loss, and unorganized neoangiogenic loops. [18–26]

Damage to the vessels can be accompanied by a lack of repair. The activation of these angiogenic signals might be present, but insufficient, meaning that there is a balance between proangiogenic and antiangiogenic pathways, not just a lack of the proangiogenic pathway. Abnormal vascular architecture and decreased capillary density may help develop decreased local metabolic stress and hypoxia. All this can stimulate fibroblasts and change matrix-regulating enzyme expression, which can lead to a vicious cycle between vascular injury and structural remodeling. [7,8,10–12,18,19,23–27]

3.2. ECM components and tissue mechanics

Fibrillar collagens, basement-membrane components, elastin, fibronectin, laminins, proteoglycans, and associated matricellular proteins are found in the extracellular matrix. Collagens I and III make up the interstitial tissues and collagen IV and laminins are prominent constituents of the basement membrane. Fibronectin (FN), proteoglycans and other proteins of the matrix help to attach and move cells, regulate tissue hydration, and bind signaling molecules. The azotea of glomeruli, tubules and interstitia of the kidney contain different components of ECM, and its location of deposition is biologically important. Major components of the ECM and selected functions are summarized in figure 1 [1-6].

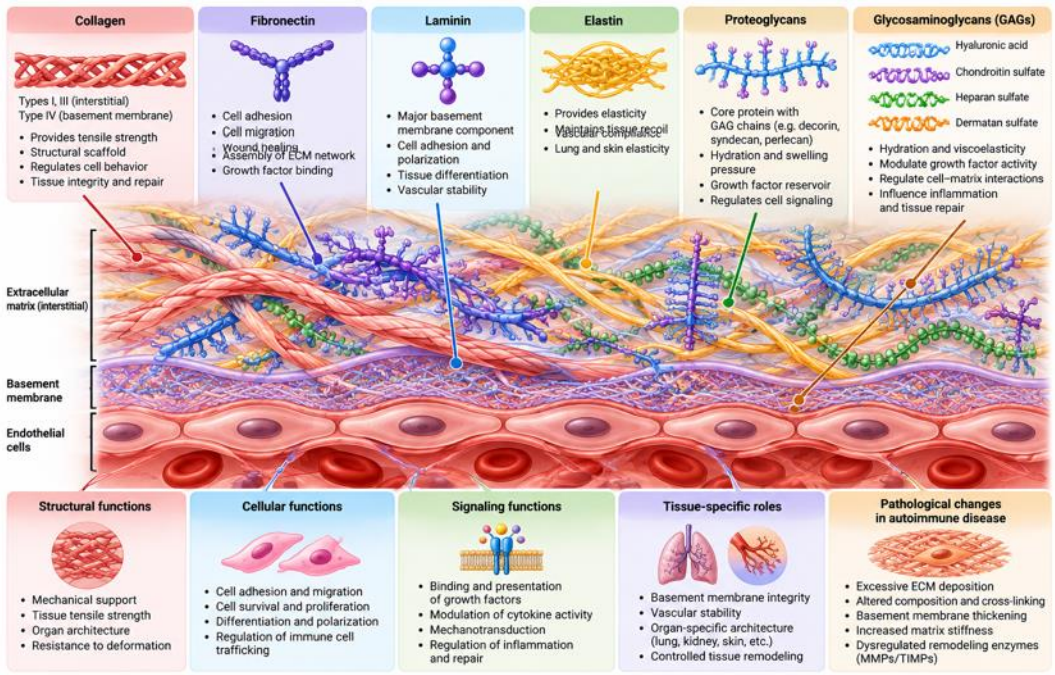


Figure 1. Schematic overview of major ECM components and selected functions.

Remodeling consists of matrix synthesis, proteolysis, cross-linking and spatial reorganization. Too much or too early deposition can affect tissue stiffness and mechano-transduction, while excessive or improper degradation can lead to the release of fragments that act as signaling molecules, and the disruption of basement membranes. Pathological accumulation or degradation of the matrix is possible; the consequences of this are related to injury stage, cell type, tissue compartment, and matrix substrate as well as enzyme activity [4–6,28–30].

3.3. Profibrotic signaling and matrix turnover

Transforming growth factor-β (TGF-β) is a prominent profibrotic mediator that has been shown to induce myofibroblast differentiation and expression of other components of the matrix and collagen. There are other pathways besides platelet derived growth factor which can modify the response, such as connective tissue growth factor, interleukin related signaling, oxidative stress and mechanical signaling. Chronic fibroblast activation increases the production of matrix, and may decrease the ability of the tissue repair. These pathways vary in terms of their contribution to specific diseases and organs. [12–14,27,31–35]

There are a number of ECM substrates that are broken down by MMPs and their activity is regulated by TIMPs. However, even though there is a higher concentration of MMP, it does not necessarily translate to a higher level of enzyme activity and a high concentration of MMP does not necessarily indicate a decrease in net fibrosis. The activity of other types of proteases, abundance of inhibitors, and availability of their substrates, localization, and enzyme activation all affect matrix turnover. Thus, the interpretation of MMP/TIMP profiles needs to be made with caution and as a specific fibrosis test alone should not be used. [4,28,29]

3.4. Bidirectional interaction between vasculature and matrix

Abnormalities in the blood vessels and the matrix may reinforce each other. Changing the endothelial barrier may impact stromal signaling and recruitment of inflammatory cells, potentially impacting endothelial adhesion, migration and survival. Additional profibrotic responses can be caused by matrix stiffening, basement-membrane disruption, hypoxia, and tissue injury. It is a model which is especially important in systemic sclerosis, but cannot be generalized to other autoimmune conditions. Different diseases, organs and stages have different dominant processes: inflammatory lesions dominate in one; microvascular abnormalities dominate in another; and chronic matrix accumulation dominates in another. These pathways are summarized in Figure 2 [7, 8, 10–14, 23, 27].

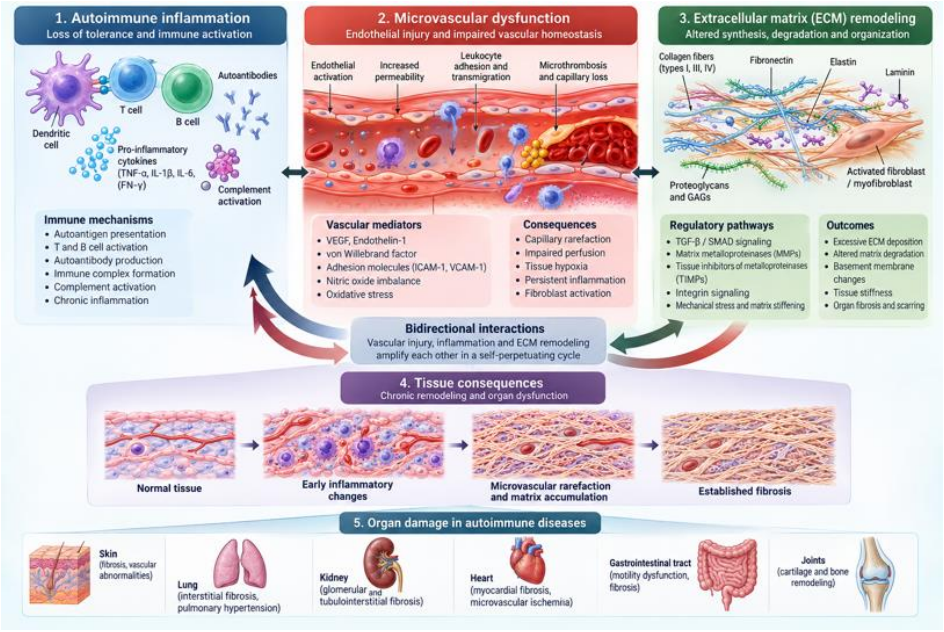


Figure 2. Conceptual model linking autoimmune inflammation, microvascular dysfunction, and extracellular matrix (ECM) remodeling.

4. Histopathological patterns in autoimmune organ damage

4.1. Systemic sclerosis: vasculopathy and fibrosis.

The characteristic features of SSc are a combination of abnormalities of small blood vessels, abnormalities of the immune system, and fibrosis (scarring) of the skin and

internal organs, which vary among people with SSc. Histological changes can be endothelial damage, intimal thickening, luminal narrowing, capillary rarefaction, collagen accumulation in the dermis and distortion of adnexal structure. The severity of inflammation is variable and fibrosis may develop without significant apparent inflammatory infiltrates. There is a close but complex relationship between vascular injury, immune activation and fibroblast biology, as highlighted by recent reviews. [7–11,20–26,34]

Nailfold videocapillaroscopy is a non-invasive method of acquiring data on peripheral microvascular architecture, which can help with the characterization of disease, but cannot entirely supplant tissue histopathology, and cannot directly measure fibrosis in internal organs. A skin biopsy will provide information on the degree of changes in the matrix for the skin that has been sampled, but not the degree of involvement in the lungs, kidneys or heart. Assessment in the organ with which the child is involved is still required [21,24–26].

4.2. Lupus nephritis: active lesions and chronic scarring

Lupus nephritis (LN) is a renal manifestation of systemic lupus erythematosus (SLE) and immune-complex mediated injury may result in inflammation and structural damage within various renal compartments. Histologic changes that may be seen in the biopsy specimen may consist of mesangial and/or endocapillary proliferation, capillary wall changes, necrosis, crescents, immune deposits, glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The clinical implications of the active lesions versus the chronic lesions differ: active inflammatory ones might be amenable to treatment, while chronic fibrosis and sclerosis signify that the structural damage is less easily reversed [15,16,30,36-41].

The focus is on activity vs chronicity; one of the main reasons for conducting studies using circulating and urinary markers. There are many different candidate markers, study designs, endpoints and evidence quality in the literature. Biomarkers should therefore be used in conjunction not in lieu of clinically indicated biopsy. Comparing active lesions with chronic structural damage, as shown in Figure 3, there are significant differences between the two [15–17,30,36,38–40,42,43].

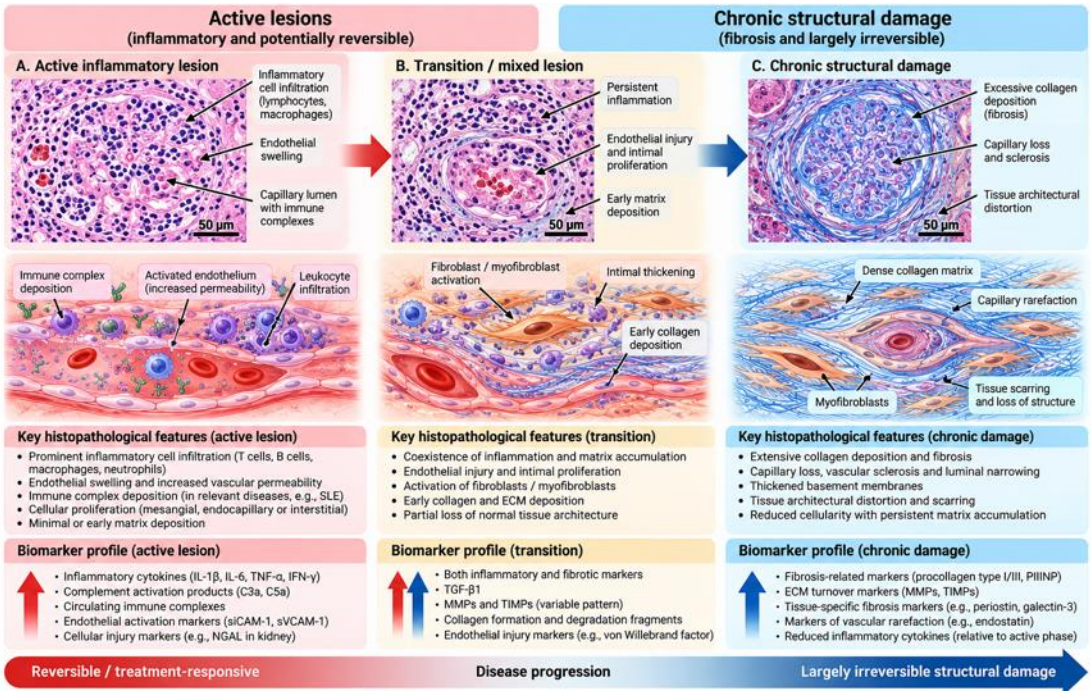


Figure 3. Schematic distinction between active lesions and chronic structural damage.

4.3. Rheumatoid arthritis: matrix degradation and synovial remodeling

In rheumatoid arthritis (RA), synovial fibrosis is an ongoing process that leads to activation of synovial fibroblasts, which leads to cartilage degradation as well as bone erosion and changes in the joint architecture. Collagen, aggrecan and other matrix molecules are broken down by matrix metalloproteinases (MMPs) and ADAMTS proteases. Damage-associated fragments of matrix may also be signals that initiate or amplify innate immune pathways. A review was published in 2026 that outlines the matrix stiffening, matrix degradation, inflammatory amplification, and reinvigorated matrix stiffening continuum as well as the potential for ECM-derived markers as disease monitors [44-48].

The relationship between ECM pathology and fibrosis is shown with RA. The type of injury to matrix may be destructive degradation, abnormal deposition, altered mechanisms or a combination of the above, depending on the tissue type. Therefore, the interpretation of biomarkers needs to be done with respect to the investigated tissue and remodeling process. [4,28,44-48]

4.4. Organ-specific interpretation

The same biomarker can mean something else when found in the skin, kidney, lungs or synovium. The glomerular basement membrane, mesangial matrix, tubular basement membrane, interstitial matrix and vascular ECM are separate ECMs in renal tissue. The lung disease associated with SSc can be characterized by both interstitial matrix accumulation and vascular disease, while cartilage and matrix degradation can be more prominent in RA than interstitial fibrosis. The pathway analysis between different diseases can help detect common pathways but not assume a threshold for a biomarker between organs. Selected disease associated patterns are compared in figure 4 [7,15,16,20,44-48].

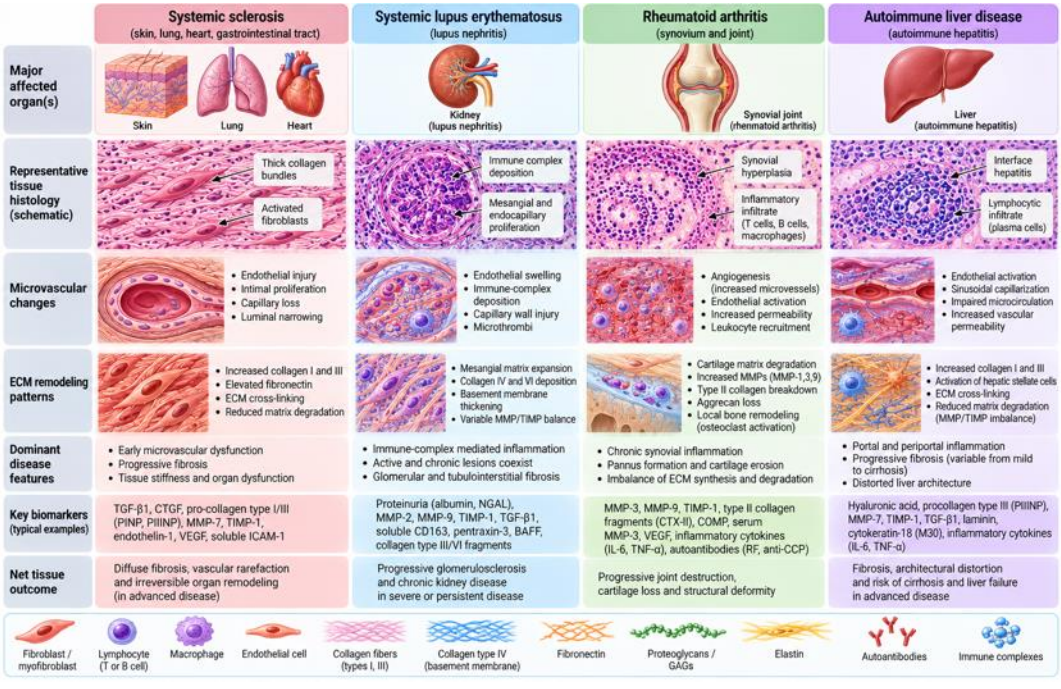


Figure 4. Cross-disease comparison of dominant tissue-remodeling patterns.

5. Biomarkers: categories, interpretation, and limitations

5.1. Collagen formation and degradation products

Collagen neoepitopes and fragments are not a direct measure of the amount of collagen in tissue but rather indicate specific collagen-formation or collagen-degradation processes. They must be able to detect remodeling, as opposed to native scars, for each analyte, assay, disease and tissue endpoint. There have been additional proposed validations of type III and VI collagen-remodeling markers to tissue endpoints in lupus nephritis published. These results will encourage further research, yet do not provide a test on its own which could be used as an alternative to biopsy [36,42,43,49,50].

5.2. MMPs and TIMPs

MMPs and TIMPs are relevant in a variety of mechanisms such as matrix turnover, basement-membrane integrity, inflammatory migration and tissue repair. Due to overlapping substrates, differences in proenzymes and active enzymes, tissue specific expression and endogenous inhibitor effects, and their clinical interpretation is complicated. The utility of a panel, representative of selected MMPs and TIMPs, is greater than one marker, however clinical utility needs to be proven in a prospective study. [4,28,29]

5.3. TGF-β and other profibrotic mediators

The involvement of the TGF-β signaling pathway in fibrotic diseases has been studied and is involved in systemic sclerosis and renal disease. The concentrations in the circulation do not necessarily reflect local activity but might also be affected by the way the samples are handled and by the tissue source of the analytes. Thus, these measurements should be considered as indirect, rather than quantitative markers of organ fibrosis along the pathways. In 2026, a pathologist-driven review of lupus nephritis biomarkers identified TGF-β1 as a candidate biomarker with supporting evidence, and emphasized the need for further studies for validation prior to clinical use [12–14,27,31–36].

5.4. Endothelial activation and angiogenesis

Candidates for the vascular markers include von Willebrand factor, soluble adhesion molecules, and mediators associated with the process of angiogenesis, such as VEGF signaling. These analytes are not specific to autoimmune vascular injury, but rather may reflect endothelial activation or some type of vascular repair. They can be affected by systemic inflammation, cardiovascular diseases, drugs and other causes of endothelial stress. For this reason, vascular biomarkers can be used in addition to clinical signs and symptoms, capillaroscopic or organ-specific evaluation in SSc. [18–20,24–26]

5.5. Urinary and circulating biomarkers in lupus nephritis

Cytokines, chemokines, complement-related analytes, immune-cell associated proteins, renal injury markers, and molecular signatures are examples of the factors studied by LN biomarker studies. The advantages of urinary biomarkers are that they could reflect kidney processes, but there can be factors that affect the concentration of the biomarker in the urine, such as filtration, tubular handling, proteinuria, renal function, and normalization of the urine. A systematic review of LN biomarkers identified the wide range of potential markers and the necessity for further validation of the markers in diagnosis, monitoring and prognosis. Another pathologist-centric evaluation of the studies also noted that many of the studies were of limited quality methodologically and that there is a need to replicate the relationship between biomarkers and lesions. [15,17,36–43]

5.6. Interpreting a biomarker panel

A biomarker panel must be in response to a specific clinical question, for example to detect active inflammation, to estimate structural fibrosis, to monitor response, or to predict progression. Having markers in multiple biological domains can have

advantages in characterization; however, it can also be expensive and create an issue of over fitting. Panels need to be prespecified, and need to be validated and use standardised assays and reference standards. They must add value, which needs to be proven and not taken for granted, over existing clinical details. The conceptual map in Figure 5 connects the classes of biomarkers to the biological domains [18–20,23,36,42,43,49,50].

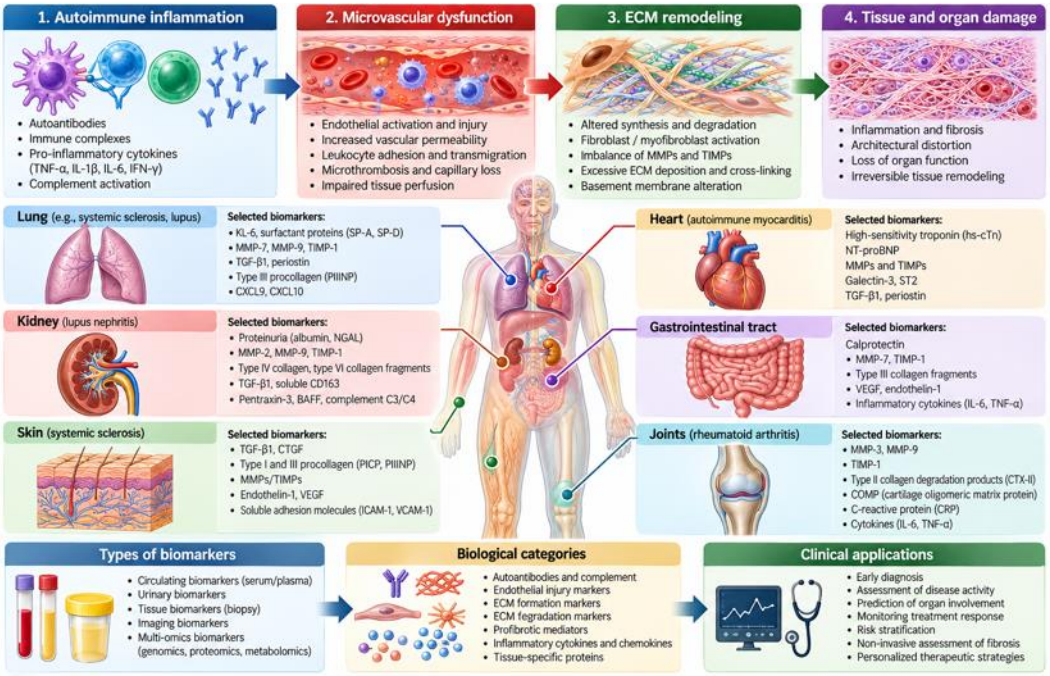


Figure 5. Conceptual biomarker map.

Table 1. Candidate biomarker classes and their interpretive role

Biomarker class	Biological domain	Potential role	Key limitation
Collagen remodeling fragments	ECM formation/degradation	Research assessment of fibrosis and matrix turnover	May not distinguish net deposition from degradation without analyte-specific validation
MMPs/TIMPs	Proteolysis and matrix regulation	Characterization of remodeling pathways	Concentration may not reflect active enzyme function
TGF-β-related mediators	Profibrotic signaling	Study of fibrotic pathway activity	Circulating level may not reflect local tissue signaling
vWF and soluble adhesion molecules	Endothelial activation	Assessment of vascular stress	Limited specificity for autoimmune vascular injury
VEGF-related mediators	Angiogenesis and vascular repair	Study of vascular repair imbalance	Levels do not directly measure functional perfusion
Urinary cytokines/renal injury proteins	Renal inflammation and injury	Potential monitoring of LN activity	Influenced by renal function, urine concentration, and assay methods
ECM fragments in RA	Cartilage/synovial matrix degradation	Potential disease monitoring and response assessment	Tissue and disease specificity are essential

These are biomarker categories that are candidates for research; they are not meant to be a list of clinically validated tests.
They must be validated for the specific analytes they need to be used with, and proven to be clinically useful [18,19,30,36,42–44,49,50].

Table 2. Histopathology and complementary assessment across selected autoimmune diseases

Disease/organ context	Representative tissue findings	Complementary assessment	Important interpretive issue
Systemic sclerosis, skin and small vessels	Dermal collagen accumulation; vascular narrowing; capillary loss	Clinical vascular assessment; nailfold videocapillaroscopy; organ-specific testing	Peripheral microvascular findings do not quantify internal-organ fibrosis
Lupus nephritis	Glomerular inflammation; immune deposits; sclerosis; tubular atrophy/interstitial fibrosis	Renal function, urine findings, serology, selected urinary biomarkers	Activity and chronicity are distinct and may coexist
Rheumatoid arthritis, synovium/joint	Synovitis; cartilage matrix degradation; erosive structural damage	Clinical disease activity; imaging; selected ECM degradation markers	Matrix degradation and fibrosis are not interchangeable processes
Autoimmune interstitial lung involvement	Inflammation and/or interstitial matrix accumulation with variable vascular changes	Pulmonary function tests and appropriate imaging	Imaging and circulating markers cannot fully substitute for tissue-specific validation

These are the conceptual similarities between the selected autoimmune diseases and are meant to be used in conjunction with the diagnostic criteria of the individual diseases and the literature [7,15,16,18–21,26,30,36,44–48].

6. Correlating histopathology with markers

Histopathology is a technique used to determine the severity, pattern and location of damage to the tissue in the sample. Biomarkers can be measured repeatedly, but are less anatomical in nature and vascular imaging or capillaroscopy give information on structure or function in selected vascular beds. When these methods do answer specific clinical questions, they are helpful when used together [15–17,21,26,30,36,42,43].

Histological activity and chronicity indices of the lupus nephritis are reference endpoints for validation of the biomarker. When assessing candidate vasculitis markers in systemic sclerosis, one should keep in mind the specific vascular features and not general disease labels or other categories. For RA, markers derived from the ECM should be compared to markers of joint damage or response to treatment that have been validated. Correlation with a histologic characteristic does not prove the applicability of a biomarker to the diagnosis instead of or to enhance the patient outcome. A schematic overview of the integrated approach of the histopathology, vascular assessment and biomarker profiles is summarized in figure 6 [15–18,30,36–50].

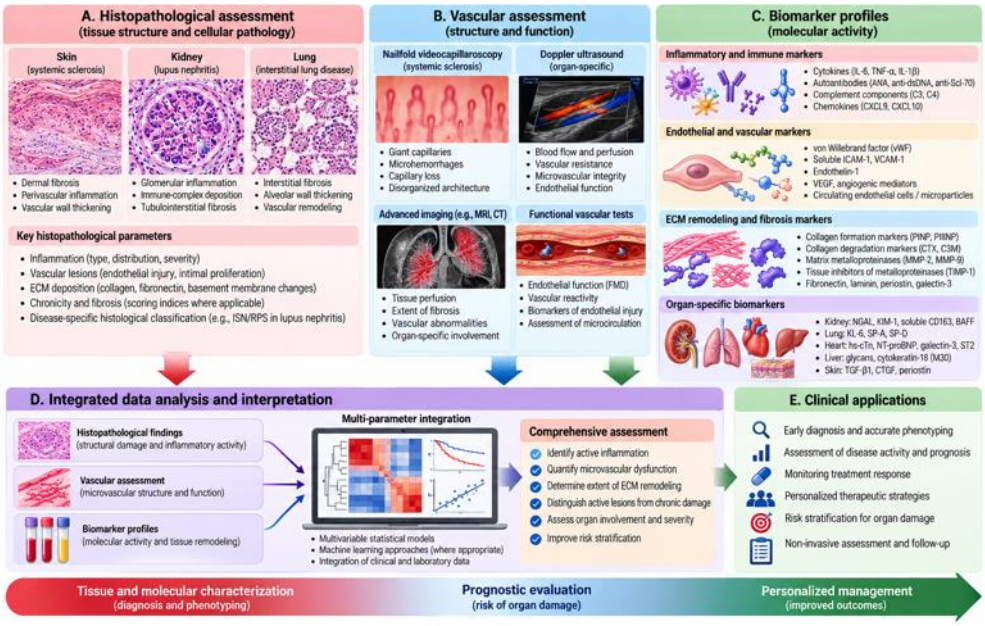


Figure 6. Integrated framework combining histopathology, vascular assessment, and biomarker profiles.

7. Evidence gaps and translational challenges

7.1. Cross-sectional designs and causal uncertainty

Cross-sectional associations do not allow for the assessment of temporal sequence and/or changes in biomarker prior to, during, and after tissue damage. Longitudinal cohorts, where repeated measurements have been taken, and clinical outcomes are well defined, are required for evaluation of predictive performance [17,36-40,42,43].

7.2. Analytical heterogeneity

Studies are hard to compare if there are differences in the assay platforms, handling of specimens, normalization procedures, reference intervals, or reporting units. Analytical validity, within-run and between-run precision, limits of detection (LOD) and the impact of relevant pre-analytical variables should be reported in biomarker studies [18,19,36,42,43].

7.3. Confounding and tissue specificity

Biomarker levels could be affected by a variety of factors, such as age, renal function, infection, cardiovascular disease, medication usage, and systemic inflammation. It is important to consider factors of dilution and renal handling when considering urinary measurements. A biomarker which works well for one organ or disease type should not be presumed to work for another type. [18,19,36,42,43]

7.4. Clinical utility and external validation

There is no clinical utility if only a statistical significance or biological plausibility. Discrimination, calibration, sensitivity and specificity and incremental value over standard clinical measures should be reported in the intended population in studies reporting discrimination. External validation and prospective evaluation of clinical impact is also needed. Lupus nephritis biomarker reviews have emphasized the heterogeneity of methods and limitations of the current evidence. Figure 7 represents a possible pathway in the validation of analytical performance towards clinical utility [17,36–40,42,43].

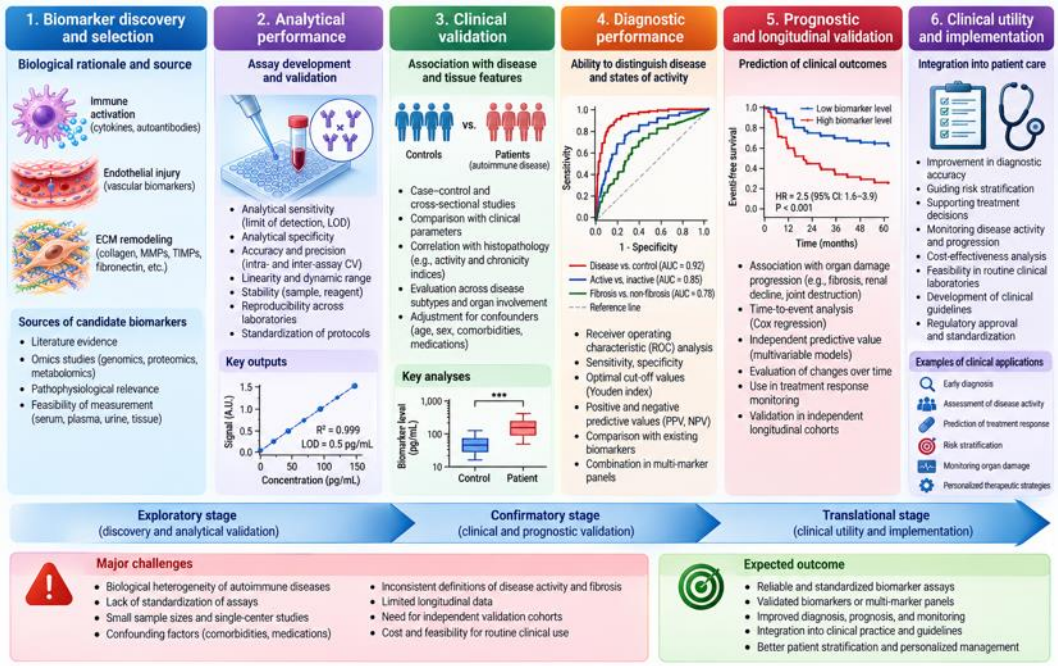


Figure 7. Developed validation pathway for candidate biomarkers, from analytical performance to clinical utility.

8. Future research priorities

Multicentre studies going forward could include uniform histopathological scoring, organ outcomes over time, and prospective collection of biomarkers. Panels should answer specific clinical questions and be composed of well-defined, biologically relevant domains (e.g., endothelial activation, inflammation, ECM turnover) and not just be a compilation of candidate analytes. There is a need for assay harmonization and external validation prior to clinical readiness [3–6,12–14,33,35,36,42,43].

Spatial transcriptomics, single cell techniques, proteomics and matrix-based molecular profiling can be used to help identify the cell types that make particular ECM components, and to help understand the difference in signals between tissue compartments. These strategies can be used to formulate and test hypotheses, but yet independent confirmation, analytical validation, and evidence for added clinical value is required prior to translation [3–6,12,33,35].

Another important aspect is to be able to separate damage caused by past occurrences from ongoing remodeling. Repeated measurement of ECM fragments that are involved in matrix formation and/or degradation, together with organ-specific clinical outcome, could be useful to elucidate these processes. The change in biomarker levels should not be viewed as a sign of histological regression or progression without validation of this relationship [12–14,27,43,49,50].

9. Conclusion

The microvascular dysfunction and the structural ECM remodeling are interrelated processes which also contribute to organ damage in autoimmune diseases, but to a varying extent depending on the disease and tissue type. This can result in capillary rarefaction, basement-membrane abnormalities, accumulation of matrix, or destruction of matrix. Although histopathology is important to classify tissue lesions, vascular assessment and biomarkers may offer complementary information regarding biological activity and/or change over time.

Promising research areas include collagen-remodeling fragments, MMP/TIMP systems, mediators of TGF-β, endothelial markers, and urinary biomarkers, with the latter areas needing further standardization and clinical validation before they can be used routinely in the clinic. While clinical translation will need to be

achieved through an integrated, organ-specific evaluation, long-term evidence, and demonstrated incremental clinical value, this will require work [3-7, 12-14, 18, 19, 27, 36, 42-44, 49, 50].

References

1. Bulow RD, Boor P. Extracellular matrix in kidney fibrosis: more than just a scaffold. J Histochem Cytochem. 2019;67(9):643-661. doi:10.1369/0022155419849388.

2. Hynes RO. The extracellular matrix: not just pretty fibrils. Science. 2009;326(5957):1216-1219. doi:10.1126/science.1176009.

3. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci. 2010;123(Pt 24):4195-4200. doi:10.1242/jcs.023820.

4. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb Perspect Biol. 2011;3(12):a005058. doi:10.1101/cshperspect.a005058.

5. Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. Nat Rev Mol Cell Biol. 2014;15:802-812. doi:10.1038/nrm3896.

6. Shoulders MD, Raines RT. Collagen structure and stability. Annu Rev Biochem. 2009;78:929-958. doi:10.1146/annurev.biochem.77.032207.120833.

7. Ko J, Noviani M, Chellamuthu VR, Albani S. The pathogenesis of systemic sclerosis: the origin of fibrosis and interlink with vasculopathy and autoimmunity. Int J Mol Sci. 2023;24(18):14287. doi:10.3390/ijms241814287.

8. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. Nat Rev Dis Primers. 2015;1:15002. doi:10.1038/nrdp.2015.2.

9. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009;360:1989-2003. doi:10.1056/NEJMra0806188.

10. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest. 2007;117(3):557-567. doi:10.1172/JCI31139.

11. Abraham DJ, Krieg T, Distler J, et al. Overview of pathogenesis of systemic sclerosis. Rheumatology (Oxford). 2009;48 Suppl 3:iii3-iii7. doi:10.1093/rheumatology/kep108.

12. Distler JHW, Györfi AH, Ramanujam M, Whitfield ML, Königshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol. 2019;15:705-730. doi:10.1038/s41584-019-0322-7.

13. Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008;214(2):199-210. doi:10.1002/path.2277.

14. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2012;18(7):1028-1040. doi:10.1038/nm.2807.

15. Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD atlas of renal pathology: lupus nephritis. Am J Kidney Dis. 2016;68(2):e1-e7. doi:10.1053/j.ajkd.2016.05.012.

16. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65(2):521-530. doi:10.1111/j.1523-1755.2004.00443.x.

17. KDIGO. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. Kidney Int. 2024;105(1S):S1-S69. doi:10.1016/j.kint.2023.09.002.

18. Fioretto BS, Rosa I, Matucci-Cerinic M, Romano E, Manetti M. Current trends in vascular biomarkers for systemic sclerosis: a narrative review. Int J Mol Sci. 2023;24(4):4097. doi:10.3390/ijms24044097.

19. Di Maggio G, Confalonieri P, Salton F, et al. Biomarkers in systemic sclerosis: an overview. Curr Issues Mol Biol. 2023;45(10):7775-7802. doi:10.3390/cimb45100490.

20. Morales-González V, Galeano-Sánchez D, Covaleda-Vargas JE, Rodriguez Y, Monsalve DM, Pardo-Rodriguez D, et al. Metabolic fingerprinting of systemic sclerosis: a systematic review. Front Mol Biosci. 2023;10:1215039. doi:10.3389/fmolb.2023.1215039.

21. Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747-1755. doi:10.1136/annrheumdis-2013-204424.

22. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573-1576.

23. Distler O, Assassi S, Cottin V, et al. Mechanisms of disease: the rationale for targeted therapies in systemic sclerosis. Nat Rev Rheumatol. 2017;13:451-464. doi:10.1038/nrrheum.2017.105.

24. Fleming JN, Nash RA, McLeod DO, et al. Capillary regeneration in scleroderma: stem cell therapy reverses phenotype? PLoS One. 2008;3(1):e1452. doi:10.1371/journal.pone.0001452.

25. Cutolo M, Sulli A, Smith V. Assessing microvascular changes in systemic sclerosis diagnosis and management. Nat Rev Rheumatol. 2010;6:578-587. doi:10.1038/nrrheum.2010.104.

26. Smith V, Herrick AL, Ingegnoli F, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev. 2020;19(3):102458. doi:10.1016/j.autrev.2020.102458.

27. Rockey DC, Bell PD, Hill JA. Fibrosis—a common pathway to organ injury and failure. N Engl J Med. 2015;372:1138-1149. doi:10.1056/NEJMra1300575.

28. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007;8:221-233. doi:10.1038/nrm2125.

29. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006;69(3):562-573. doi:10.1016/j.cardiores.2005.12.002.

30. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018;93(4):789-796. doi:10.1016/j.kint.2017.11.023.

31. Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. FASEB J. 2004;18(7):816-827. doi:10.1096/fj.03-1273rev.

32. Verrecchia F, Mauviel A. Transforming growth factor-beta signaling through the Smad pathway: role in extracellular matrix gene expression and regulation. J Invest Dermatol. 2002;118(2):211-215. doi:10.1046/j.1523-1747.2002.01641.x.

33. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature. 2003;425(6958):577-584. doi:10.1038/nature02006.

34. Jinnin M. Mechanisms of skin fibrosis in systemic sclerosis. J Dermatol. 2010;37(1):11-25. doi:10.1111/j.1346-8138.2009.00738.x.

35. Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest. 2003;112(12):1776-1784. doi:10.1172/JCI20530.

36. Querin V, Palazzo L, Fogo AB, Haas M, Jayne DRW, Lightstone L, et al. Biomarkers of lupus nephritis histopathology: where do we stand? Arthritis Rheumatol. 2026;78(3):548-557. doi:10.1002/art.43427.

37. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83(1):15-29. doi:10.1136/ard-2023-224762.

38. Parikh SV, Almaani S, Brodsky S, Rovin BH. Update on lupus nephritis: core curriculum 2020. Am J Kidney Dis. 2020;76(2):265-281. doi:10.1053/j.ajkd.2019.10.017.

39. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835. doi:10.2215/CJN.05780616.

40. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. Kidney Int. 2021;100(4):753-779. doi:10.1016/j.kint.2021.05.015.

41. Furie R, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis. N Engl J Med. 2022;386:1117-1128. doi:10.1056/NEJMoa2116025.

42. Palazzo L, Lindblom J, Mohan C, Parodis I. Current insights on biomarkers in lupus nephritis: a systematic review of the literature. J Clin Med. 2022;11(19):5759. doi:10.3390/jcm11195759.

43. Guimarães JADR, Furtado SC, Lucas ACS, Mori B, Barcellos JFM. Diagnostic test accuracy of novel biomarkers for lupus nephritis—an overview of systematic reviews. PLoS One. 2022;17(10):e0275016. doi:10.1371/journal.pone.0275016.

44. Yang Q, Xu Y, Xu J, Zhang J, Yan H, Xiao N, et al. Extracellular matrix remodeling in the pathogenesis and therapeutic strategies of rheumatoid arthritis. Clin Exp Med. 2026;26:136. doi:10.1007/s10238-026-02072-z.

45. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity. 2017;46(2):183-196. doi:10.1016/j.immuni.2017.02.006.

46. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023-2038. doi:10.1016/S0140-6736(16)30173-8.

47. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205-2219. doi:10.1056/NEJMra1004965.

48. Pap T, Korb-Pap A. Cartilage damage in osteoarthritis and rheumatoid arthritis—two unequal siblings. Nat Rev Rheumatol. 2015;11:606-615. doi:10.1038/nrrheum.2015.95.

49. Genovese F, Akhgar A, Lim SS, Farris AB, Battle M, Cobb J, et al. Collagen type III and VI remodeling biomarkers are associated with kidney fibrosis in lupus nephritis. Kidney360. 2021;2(9):1473-1481. doi:10.34067/KID.0001132021.

50. Caster DJ, Merchant ML. Collagen remodeling biomarkers in lupus nephritis. Kidney360. 2021;2(9):1395-1398. doi:10.34067/KID.0004732021.