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Review

Biomarkers in Systemic Sclerosis

Claudio Karsulovic [1,2,*] and Lia Hojman [2,3]

[1] Rheumatology Section, Internal Medicine Department, Facultad de Medicina Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago P.O. Box 7630000, Chile
[2] Investigation in Dermatology and Autoimmunity—IDeA Lab, Instituto de Ciencias e Innovación en Medicina, Universidad del Desarrollo, Santiago P.O. Box 7630000, Chile; lhojman@alemana.cl
[3] Dermatology Section, Surgery Department, Facultad de Medicina Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago P.O. Box 7630000, Chile
* Correspondence: ckarsulovic@alemana.cl; Tel.: +562-22101111

Abstract: Systemic sclerosis (SSc) is a complex autoimmune disease characterized by vasculopathy, immune dysregulation, and progressive fibrosis affecting the skin and internal organs. Pulmonary complications, including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), are major contributors to morbidity and mortality, while skin fibrosis remains a hallmark of disease heterogeneity. Despite advances in understanding SSc pathogenesis, early diagnosis and timely therapeutic intervention remain challenging due to the rapid progression of inflammation and the narrow window before irreversible fibrosis occurs. The identification of reliable biomarkers is crucial for improving diagnosis, monitoring disease activity, and guiding treatment decisions in SSc. While autoantibodies are well-established diagnostic tools, this review focused on non-autoantibody biomarkers, including soluble proteins, cytokines, chemokines, epigenetic modifiers, and oxidative stress indicators. These biomarkers reflect diverse pathogenic mechanisms such as endothelial injury, fibroblast activation, immune signaling, and extracellular matrix remodeling. By examining the available evidence across both clinical and preclinical studies, this review provides an updated overview of molecular markers involved in inflammation and fibrosis in SSc. Understanding their biological significance and therapeutic potential may improve risk stratification, guide targeted interventions, and ultimately contribute to the development of precision medicine strategies in systemic sclerosis.

Keywords: systemic sclerosis; biomarkers; KL-6; IL-6; skin

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1. Introduction

Systemic sclerosis (SSc), commonly referred to as scleroderma, is a multifaceted autoimmune disease characterized by vasculopathy, immune system dysregulation, and progressive fibrosis affecting the skin and internal organs. Among the clinical manifestations, cutaneous and pulmonary involvement are the most prevalent and contribute significantly to the disease's morbidity and mortality. Pulmonary complications, such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), are the leading causes of death in SSc, while skin fibrosis remains a defining feature of the disease's heterogeneity and progression. Despite advances in understanding SSc pathogenesis, early diagnosis and timely therapeutic intervention remain challenging due to the rapid progression of the inflammatory phase and the limited window of opportunity before irreversible fibrosis sets in. The identification of reliable biomarkers is crucial for improving the early diagnosis, monitoring disease activity, and tailoring therapeutic interventions in SSc. Biomarkers can serve as indicators of pathological processes and provide insights

into the mechanisms driving the disease. While autoantibodies, such as anti-Scl-70 and anti-centromere antibodies, have long been established as diagnostic tools and predictors of specific clinical phenotypes, this review focused on non-autoantibody biomarkers. Specifically, we examined soluble proteins, cytokines, chemokines, epigenetic regulators, and other molecular indicators derived from studies in patient populations and animal models. These biomarkers not only reflect pathophysiological changes but also hold promise as potential therapeutic targets. Established examples include Krebs von den Lungen-6 (KL-6), a mucin-like glycoprotein associated with ILD severity; soluble CD146 (sCD146), a marker of endothelial dysfunction and fibrosis; and galectin-3, a protein implicated in cardiac fibrosis and systemic inflammation. Other molecules, such as Gremlin-1, insulin-like growth factor binding protein-7 (IGFBP7), S100A6, periostin, and malondialdehyde (MDA), are also explored for their potential roles in reflecting fibrotic progression, vascular remodeling, oxidative stress, and immune activation. Many of these candidates are currently under investigation in preclinical models or observational cohorts, contributing to a growing body of evidence on their potential utility in clinical settings. The exclusion of autoantibodies as biomarkers in this review is deliberate, aiming to emphasize less-explored molecular players with both diagnostic and therapeutic potential. While autoantibodies have been instrumental in defining SSc subtypes and predicting organ involvement, they offer limited insight into the dynamic and multifactorial nature of the disease. By focusing on non-autoantibody biomarkers, this review seeks to highlight molecules that capture broader physiological alterations and represent viable targets for intervention in both early and advanced stages of the disease. This review synthesizes current knowledge on non-autoantibody biomarkers in SSc, integrating established findings with emerging data. By examining their clinical relevance, biological roles, and therapeutic potential, we aimed to improve diagnostic precision and contribute to innovation in systemic sclerosis management. The ultimate goal is to enhance early detection, guide treatment strategies, and identify meaningful targets to improve patient outcomes.

2. Biomarkers in Systemic Sclerosis

2.1. IL-6

Interleukin-6 (IL-6) is a multifunctional cytokine that plays a critical role in the pathogenesis of systemic sclerosis (SSc), a complex autoimmune disease characterized by fibrosis, vascular dysfunction, and immune dysregulation (Table 1) [1]. IL-6 is produced by various cell types, including fibroblasts, T cells, B cells, and macrophages, and is involved in both inflammatory responses and fibrotic processes [2]. In SSc, elevated levels of IL-6 have been associated with disease severity and progression since fibroblasts produce IL-6 in response to inflammatory stimuli, which in turn promotes further fibroblast activation and collagen production [3]. This autocrine loop contributes significantly to the fibrotic process characteristic of the disease. Additionally, IL-6 has been shown to stimulate the production of other profibrotic factors, such as platelet-derived growth factor (PDGF) and procollagen type I, further exacerbating the fibrotic response [3]. The role of IL-6 in SSc extends beyond fibroblast activation. It is also implicated in the regulation of immune responses, such as the differentiation and activation of T cells, particularly Th17 cells, which are associated with inflammation and tissue damage in autoimmune diseases [4]. The interplay between IL-6 and other cytokines in the inflammatory milieu of SSc underscores its importance in the disease's pathophysiology and its therapeutic benefits [5]. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has shown promise in clinical trials, leading to improvements in skin sclerosis and pulmonary fibrosis in SSc patients [6]. The blockade of IL-6 signaling not only reduces inflammation but also appears to reverse TGF-β activation, a key

pathway involved in fibrosis [7,8]. This suggests that IL-6 plays a dual role in promoting both inflammation and fibrosis in SSc, making it a potential therapeutic target.

Table 1. Comprehensive list of markers studied in systemic sclerosis.

Biomarker	Protein Type	Biological Function	Possible Role in SSc
MCP-1 (CCL2)	Chemokine	Monocyte and macrophage recruitment	Inflammation and fibrosis in skin and lung
KL-6	Glycoprotein	Alveolar injury marker	Indicator of interstitial lung disease in SSc
TGF-β	Cytokine	Induces fibroblast differentiation	Key mediator of fibrosis in SSc
Serum amyloid A (SAA)	Acute-phase protein	Inflammatory response	Associated with ILD and PAH in SSc
Soluble CD146	Glycoprotein	Endothelial function and angiogenesis	Indicator of ILD and endothelial dysfunction
CXCL4	Chemokine	Inflammation and fibrosis	Associated with ILD and PAH in SSc
sST2	Soluble receptor	Modulates IL-33	Predicts progressive vascular fibrosis in SSc
Endothelin-1	Peptide	Vasoconstriction and fibrosis	Contributes to PAH and vascular dysfunction
PAI-1	Serine protease inhibitor	Inhibits fibrinolysis	Promotes fibrosis in skin and lung
SPARC	Matricellular protein	ECM remodeling	Activates TGF-β and promotes fibrosis
Fibronectin	Glycoprotein	Cell adhesion and ECM	Altered in SSc fibroblasts
Periostin	Matricellular protein	Collagen interaction	Indicator of fibrosis
Tenascin-C	Glycoprotein	ECM maintenance	Contributes to pulmonary fibrosis
TET2	Epigenetic regulator	DNA demethylation	Downregulated in SSc fibroblasts
Cytohesin-2	Nucleotide exchange factor	Fibroblast migration	Enhances focal adhesion in SSc
miR-21	MicroRNA	Post-transcriptional regulation	Activates TGF-β and promotes fibrosis
miR-29	MicroRNA	Collagen regulation	Downregulated in SSc, promoting fibrosis
STING	Adaptor protein	Innate immune response	Excessive activation in SSc
(94)IP-10 (CXCL10)	Chemokine	Th1 lymphocyte attraction	Associated with pulmonary fibrosis
CCL18	Chemokine	Fibroblast activation	Associated with ILD severity and mortality
CX3CL1	Chemokine	Monocyte recruitment	Promotes fibroblast activation
HSP47	Chaperone	Collagen maturation	Promotes ECM accumulation
TWEAK	Cytokine	Fibroblast proliferation	Enhances vascular damage

Table 1. *Cont.*

Biomarker	Protein Type	Biological Function	Possible Role in SSc
Angiopoietin-2	Growth factor	Vascular destabilization	Biomarker of PAH in SSc
VEGF	Growth factor	Angiogenesis	Elevated in SSc but ineffective
NOX4	Enzyme	ROS production	Drives fibrosis
8-Isoprostane	Oxidative stress marker	Lipid peroxidation	Elevated in SSc
Leptin	Hormone	Energy regulation	Promotes inflammatory activation
Adiponectin	Hormone	Anti-inflammatory effect	Elevated in severe fibrosis
Gremlin-1	Protein	BMP regulation	Enhances TGF-β-mediated fibrosis
IGFBP7	Protein	IGF modulation	Associated with pulmonary fibrosis
IGF-1	Growth factor	Fibroblast differentiation	Promotes fibrosis
Galectin-3	Lectin	Immune activation and fibrosis	Indicator of cardiac involvement
Osteopontin	Glycoprotein	Cell adhesion	Linked to PAH and fibrosis
S100A6	Protein	Cell migration	Associated with fibroblast proliferation
FSTL1	Glycoprotein	TGF-β enhancer	Promotes fibrosis
NETosis	Cellular process	Neutrophil extracellular traps release	Promotes endothelial damage
LRG1	Protein	Endothelial dysfunction modulator	Associated with vascular fibrosis

2.2. MCP-1

Monocyte Chemoattractant Protein-1 (MCP-1), also known as CCL2, is a chemokine that plays a significant role in the pathogenesis of SSc (Table 1). It is primarily involved in the recruitment of monocytes and macrophages to sites of inflammation, contributing to the inflammatory and fibrotic processes characteristic of the disease [9]. In SSc, elevated levels of MCP-1 have been associated with disease activity [10]. MCP-1 is produced by various cell types, including fibroblasts, endothelial cells, and macrophages, in response to inflammatory stimuli. This production is often upregulated in the skin and lungs of SSc patients, correlating with the extent of fibrosis and vascular damage [11]. Some studies have shown that MCP-1 levels are significantly higher in the serum of SSc patients compared with healthy controls, and these levels correlate with clinical manifestations such as skin thickening and pulmonary involvement [10]. The MCP-1/CCR2 signaling axis is crucial in mediating the recruitment of monocytes to inflamed tissues. Upon binding to its receptor CCR2, MCP-1 activates various intracellular signaling pathways that promote monocyte migration and activation, leading to the accumulation of inflammatory cells in affected tissues [12,13]. This process is particularly relevant in SSc, where the influx of monocytes contributes to the chronic inflammatory environment and subsequent fibrosis. For example, MCP-1 has been shown to stimulate collagen production by fibroblasts, enhancing the fibrotic response [14]. Moreover, MCP-1 is implicated in the development of vascular complications in SSc [10]. Elevated MCP-1 levels have been associated with pulmonary arterial hypertension (PAH), a severe complication of SSc characterized by increased blood

pressure in the pulmonary arteries [10]. The recruitment of inflammatory cells to the pulmonary vasculature can lead to vascular remodeling and dysfunction, contributing to the pathogenesis of PAH in SSc patients [15,16]. These findings emphasize the importance of MCP-1 as a target for therapeutic intervention. Recent studies have explored the therapeutic potential of targeting the MCP-1/CCR2 pathway in SSc [17]. The signaling axis has shown promise in preclinical models, suggesting that blocking MCP-1 or its receptor could mitigate the inflammatory and fibrotic processes associated with SSc [18]. Such approaches may provide new avenues for treatment, particularly for patients with progressive disease.

2.3. KL-6

Krebs von den Lungen-6 is a mucin-like glycoprotein primarily expressed on the surface of type II alveolar epithelial cells. It has emerged as a significant biomarker for interstitial lung disease (ILD), particularly in the context of SSc (Table 1). The elevation of KL-6 levels in serum is indicative of lung injury and has been correlated with disease severity and progression in SSc-associated ILD [19]. Research has demonstrated that KL-6 concentrations correlate negatively with pulmonary function parameters such as forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) [20]. It has been reported that reduced FVC and DLCO were significantly associated with increased KL-6 levels in SSc patients with ILD ($r = -0.47$ and $r = -0.58$, respectively; both $p < 0.05$) [21]. Also found that serum KL-6 levels at diagnosis could serve as a predictive biomarker for progression to end-stage lung disease, further emphasizing its prognostic value [21]. KL-6 has been recognized for its role in the fibrotic process, as it is secreted in response to lung injury and is involved in the regulation of collagen expression and myofibroblast differentiation [22,23]. Kuwana et al. identified a baseline KL-6 level > 1273 U/mL as predictive of more severe lung lesions in early SSc and demonstrated that this cutoff could help stratify patients by ILD progression risk [24]. Similarly, Stock et al. showed that KL-6 levels exceeding 1472 U/mL were predictive of a $\geq$15% decline in DLCO over a 2-year period, highlighting KL-6 as a reliable predictor of functional decline in SSc-ILD [25]. Elevated KL-6 levels have been associated with the extent of lung fibrosis and disease progression in other connective tissue diseases, suggesting that it may serve as a useful biomarker for monitoring disease activity [26]. In a prospective study with a 2-year follow-up, KL-6 was identified as a predictor of early progression in SSc-related ILD, outperforming other biomarkers such as CCL-18 [27]. The utility of KL-6 extends beyond SSc, as it has been studied in various interstitial lung diseases, including idiopathic pulmonary fibrosis (IPF) and other connective tissue diseases. For example, KL-6 levels have been shown to correlate with high-resolution computed tomography (HRCT) scores in patients with ILD, indicating its potential as a diagnostic tool [28,29]. Furthermore, KL-6 has been suggested as a biomarker for distinguishing between ILD and other common lung diseases, enhancing its clinical relevance [27].

2.4. TGF-β

Transforming growth factor-beta is a pivotal cytokine that plays a central role in the pathogenesis of SSc. The TGF-β signaling pathway is notably overactive in SSc, contributing significantly to the fibrotic processes that define the disease [30] (Table 1). TGF-β induces the activation of fibroblasts, leading to their transformation into myofibroblasts, which are responsible for excessive collagen production and extracellular matrix (ECM) deposition [31]. This process is mediated through both canonical (Smad-dependent) and non-canonical (Smad-independent) signaling pathways. The canonical pathway involves the phosphorylation of Smad proteins, which translocate to the nucleus and regulate the expression of fibrotic genes, while the non-canonical pathways involve various signaling

cascades, including those mediated by reactive oxygen species (ROS) and Wnt signaling [32,33]. Some studies have shown that TGF-β levels correlate with disease activity in SSc patients. Elevated TGF-β expression has been observed in the skin and lungs of individuals with SSc, and this elevation is associated with the severity of fibrosis [34]. Inhibition of the TGF-β pathway has been proposed as a therapeutic strategy for SSc, with studies showing that targeting TGF-β signaling can ameliorate fibrosis in experimental models of the disease [35]. In other connective tissue diseases, it has been shown to stimulate the production of connective tissue growth factor (CTGF), which further amplifies fibrotic responses and promotes ECM accumulation [36]. Moreover, TGF-β can induce endothelial-to-mesenchymal transition (EndMT), a process that contributes to vascular dysfunction and fibrosis in SSc [37,38]. The interplay between TGF-β and other signaling pathways is also critical in the context of SSc. For example, TGF-β has been shown to interact with Wnt signaling, enhancing its profibrotic effects [39]. Additionally, the reciprocal regulation between TGF-β and ROS suggests a feedback loop that perpetuates fibrogenesis, as ROS can activate TGF-β signaling, further driving fibrosis [40,41]. Recent studies have explored the therapeutic potential of targeting TGF-β signaling in SSc. Pharmacological agents that inhibit TGF-β receptor activity or downstream signaling pathways have demonstrated antifibrotic effects in preclinical models [41,42].

2.5. Serum Amyloid A

Serum amyloid A (SAA) is an acute-phase protein that plays a significant role in the inflammatory response and has been studied as a potential biomarker in various diseases, including SSc and its pulmonary manifestations (Table 1). Elevated levels of SAA have been associated with disease activity and organ involvement, particularly in patients with interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) [43]. SAA levels can reflect the extent of inflammation and tissue damage, showing that elevated SAA levels correlate with increased disease severity and can serve as a prognostic marker for pulmonary complications [43]. In this cohort of SSc patients, higher serum SAA concentrations were found to be associated with the presence of ILD, suggesting its utility in monitoring lung involvement [43]. Moreover, SAA has been implicated in the pathogenesis of ILD. It is believed that SAA may contribute to the fibrotic process by promoting the activation of fibroblasts and the deposition of extracellular matrix components. SAA has been studied in other forms of ILD. Elevated SAA levels have been observed in patients with idiopathic pulmonary fibrosis (IPF) and other connective tissue disease-associated lung diseases, indicating its broader relevance as a biomarker for lung injury [44]. The correlation between SAA levels and lung function parameters, such as forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO), further supports its potential as a non-invasive marker for assessing lung involvement in various interstitial lung diseases [43]. Furthermore, SAA levels can be influenced by various factors, including systemic inflammation and comorbidities, which may complicate their interpretation in clinical practice [45]. Importantly, SAA is largely regulated by upstream IL-6 signaling, and its elevation may primarily reflect IL-6-driven inflammation rather than direct pathogenic activity. Indeed, IL-6 blockade with tocilizumab has been shown to reduce SAA levels and improve lung outcomes in SSc patients [46,47].

2.6. Soluble CD146

Soluble CD146 (sCD146) is a glycoprotein that has garnered attention as a potential biomarker in SSc, particularly in relation to lung involvement [48] (Table 1). CD146, also known as melanoma cell adhesion molecule (MCAM), is primarily expressed on endothelial cells and plays a crucial role in cell adhesion, migration, and angiogenesis. The soluble

form of CD146 is released into circulation and has been implicated in various inflammatory and fibrotic processes associated with SSc [49]. Elevated levels of sCD146 have been correlated with disease activity and severity in SSc patients, particularly those with interstitial lung disease (ILD) [49]. This correlation suggests that sCD146 could be utilized to monitor disease progression and therapeutic responses in patients with SSc-related lung involvement. The generation of sCD146 can arise from both the shedding and alternative splicing of the primary transcript, with maybe distinct roles in the pathophysiology of SSc [50]. Moreover, the role of sCD146 extends beyond mere biomarker potential; it may also be involved in the fibrotic process itself since the protein has been shown to act as a growth factor in various angiogenic and inflammation-related pathologies, suggesting that it could contribute to the mechanisms driving fibrosis in SSc [51]. This dual role as both a biomarker and a participant in disease pathology makes sCD146 a compelling target for further research [52].

2.7. CXCL4

CXCL4, also known as platelet factor 4, is a chemokine that has emerged as a significant biomarker in SSc. Elevated levels of CXCL4 have been associated with various clinical manifestations of the disease, including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) [53] (Table 1). CXCL4 has been shown to play a crucial role in pathogenesis by influencing inflammatory and fibrotic processes. Circulating CXCL4 levels are increased in SSc patients and correlate with the progression of heart and lung disease, suggesting its potential as a biomarker for monitoring disease activity [54]. Moreover, changes in plasma CXCL4 levels were associated with improvements in lung function in patients receiving immunosuppressive therapy for SSc-related ILD [55]. Such correlations highlight the utility of CXCL4 in assessing therapeutic responses and disease progression. Furthermore, CXCL4 has been implicated in the fibrotic phenomenon associated with SSc. It is known to promote fibroblast activation and collagen production, contributing to the excessive fibrosis seen in SSc patients [56]. The chemokine's ability to trigger monocytes and macrophages to produce platelet-derived growth factor (PDGF-BB) further underscores its role in the fibrotic cascade [56,57]. Additionally, CXCL4 has been shown to induce endothelial-to-mesenchymal transition, a process that facilitates fibrosis and vascular remodeling [56]. The immune-modulatory functions of CXCL4 extend beyond fibrosis; it also influences T-cell responses. CXCL4 drives CD4 T cells to produce interleukin-17 (IL-17), linking it to Th17-mediated inflammation, which is often observed in SSc [56]. This Th17 skewing is significant, as it is associated with the inflammatory milieu in SSc and contributes to the disease's progression. Moreover, CXCL4 has been identified as a potential marker for predicting disease prognosis since anti-CXCL4 antibodies are present in SSc patients and correlate with the type I interferon signature, which is characteristic of a subset of SSc patients with more severe disease [58].

2.8. sST2

Soluble suppression of tumorigenicity 2 (sST2) is a member of the interleukin-1 receptor family. It is primarily recognized for its role in inflammation and fibrosis, particularly in the context of cardiovascular and pulmonary complications associated with SSc [59] (Table 1). It has been shown that elevated levels of sST2 are associated with disease severity and progression in SSc patients, where sST2 levels were significantly higher in patients with limited cutaneous systemic sclerosis (lcSSc) after nine years of disease compared with those with stable disease, indicating its potential as a biomarker for progressive vascular fibrosis [60]. This correlation suggests that sST2 may reflect the underlying pathophysiological processes in SSc, particularly those related to vascular remodeling and fibrosis. The

role of sST2 extends beyond mere correlation with disease severity; it is also involved in the inflammatory response. Elevated sST2 levels have been linked to increased activity of interleukin-33 (IL-33), a cytokine that plays a critical role in promoting inflammation and fibrosis in SSc. The interaction between IL-33 and sST2 is complex, as sST2 acts as a decoy receptor for IL-33, potentially modulating its effects on inflammation and fibrosis [61]. Beyond its implications for vascular and fibrotic processes, sST2 has been associated with cardiac involvement in SSc. Elevated sST2 levels have been correlated with adverse cardiovascular events, making it a potential prognostic marker for cardiac complications in SSc patients [62]. sST2 has been shown to predict mortality in patients with heart failure, which may be relevant for SSc patients who often experience cardiac manifestations [63]. Furthermore, sST2 has been shown to reflect hemodynamic stress and pulmonary congestion, indicating its broader relevance in assessing lung involvement. Also, increased sST2 levels have been associated with pulmonary hypertension, suggesting that it may serve as a biomarker for assessing pulmonary vascular health in SSc patients [64].

2.9. Endotelin-1

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide. Elevated levels of ET-1 have been consistently observed in SSc patients, correlating with disease severity and the presence of vascular complications such as pulmonary arterial hypertension (PAH) and digital ulcers [65] (Table 1). The role of ET-1 in SSc extends beyond its vasoconstrictive properties. It is involved in promoting inflammation and fibrosis, contributing to the excessive accumulation of extracellular matrix (ECM) components characteristic of SSc since ET-1 stimulates fibroblast proliferation and collagen synthesis, thereby enhancing the fibrotic response [66]. This profibrotic effect is mediated through the activation of endothelin receptors, primarily the endothelin type A (ETA) receptor, which has been shown to be upregulated in SSc fibroblasts [67]. The interaction between ET-1 and its receptors leads to the activation of signaling pathways that promote myofibroblast differentiation, a key process in the development of fibrosis [68]. Clinical studies have demonstrated that antagonism of the endothelin pathway can have beneficial effects on SSc. Bosentan, an oral dual endothelin receptor antagonist, has been shown to reduce the incidence of new digital ulcers in patients with SSc, highlighting the therapeutic potential of targeting ET-1 signaling [69]. Additionally, bosentan has been associated with improvements in pulmonary function and a reduction in the progression of pulmonary hypertension in SSc patients [70]. However, the effects of endothelin receptor antagonists on skin fibrosis remain less clear, with some studies indicating limited efficacy in this regard [71]. The involvement of ET-1 in the pathogenesis of SSc is based also on the interaction with transforming growth factor-beta (TGF-β), another key cytokine in SSc, to enhance fibrotic processes [72]. This interaction suggests a complex network of signaling pathways that contribute to the disease's progression, where ET-1 not only acts as a vasoconstrictor but also as a mediator of fibrosis and inflammation. Moreover, the expression of ET-1 and its receptors has been observed in various cell types involved in SSc, including endothelial cells, fibroblasts, and immune cells [73].

3. Other Biomarkers in Systemic Sclerosis

3.1. Extracellular Matrix Biomarkers in Systemic Sclerosis

The extracellular matrix (ECM) plays a pivotal role in the pathogenesis of systemic sclerosis (SSc), where excessive fibrosis and abnormal tissue remodeling drive disease progression. Several ECM-related proteins have been implicated in SSc, including plasminogen activator inhibitor-1 (PAI-1), secreted protein acidic and rich in cysteine (SPARC), and various collagen-associated molecules. PAI-1 is a serine protease inhibitor that disrupts fibrinolysis by inhibiting tPA and uPA, leading to excessive ECM deposition and

fibrosis [74]. Elevated PAI-1 levels have been observed in the epidermis and endothelium of SSc patients, suggesting a role in fibrosis and vascular abnormalities [75]. Additionally, increased PAI-1 expression has been linked to diminished lung function, indicating its involvement in pulmonary fibrosis [75]. These findings highlight the potential of PAI-1 as a biomarker for disease activity in SSc, particularly concerning skin and pulmonary involvement [76]. SPARC, also known as osteonectin, is a protein that regulates ECM remodeling and collagen turnover. Increased SPARC expression in SSc fibroblasts enhances TGF-β signaling, leading to myofibroblast differentiation and excessive collagen production [77]. Additionally, SPARC has been linked to macrophage activation and endothelial dysfunction, highlighting its role in both inflammation and fibrosis [78]. Beyond these, dysregulated ECM proteins such as fibronectin, periostin, and tenascin-C contribute to the fibrotic response by altering fibroblast signaling and ECM integrity [79,80]. Clinical studies suggest that targeting PAI-1 and SPARC signaling pathways could be promising strategies for reducing fibrosis and restoring ECM balance in SSc [81] (Table 1).

3.2. Gene Activity Modifiers in Systemic Sclerosis

Epigenetic modifications and post-transcriptional regulation play critical roles in the pathogenesis of SSc. Among the most relevant genetic modulators in SSc are TET2 (ten-eleven translocation 2), cytohesin-2, and various microRNAs (miRNAs). TET2 is an epigenetic regulator involved in DNA demethylation, and its downregulation in SSc fibroblasts has been associated with hypermethylation of antifibrotic genes, leading to excessive collagen deposition and myofibroblast activation [82]. Cytohesin-2, a guanine nucleotide exchange factor, plays a role in fibroblast migration and ECM remodeling through the activation of ARF (ADP-ribosylation factor) GTPases [83,84]. Increased cytohesin-2 expression in SSc fibroblasts promotes paxillin-mediated focal adhesion, reinforcing the profibrotic phenotype [85]. Additionally, several miRNAs have been identified as key regulators of fibrosis and immune activation in SSc. miR-21, for instance, enhances TGF-β-driven fibroblast activation [86], while miR-29, which is downregulated in SSc, acts as a negative regulator of collagen production [87,88]. Other studies have also highlighted the STING pathway, which amplifies type I interferon responses and contributes to fibrosis via NF-κB signaling [89] (Table 1).

3.3. Cytokines and Chemokines in Systemic Sclerosis

The inflammatory landscape of SSc is shaped by a complex network of cytokines and chemokines that drive immune dysregulation. IP-10 (CXCL10), a chemokine-induced by interferon-gamma, is a potent attractant for Th1 lymphocytes and contributes to chronic immune activation [90]. Increased serum levels of IP-10 have been linked to pulmonary fibrosis and digital ulcers, suggesting its potential as a biomarker for disease progression [91]. Similarly, CCL18 (pulmonary and activation-regulated chemokine, PARC) is overexpressed in alternatively activated macrophages in SSc, promoting fibroblast proliferation and collagen deposition [92]. Elevated CCL18 levels in SSc patients correlate with lung fibrosis severity and increased mortality, underscoring its prognostic significance [93]. In addition to these chemokines, the CX3CL1-CX3CR1 axis facilitates monocyte recruitment and fibroblast activation, exacerbating the fibrotic process [94,95]. Emerging evidence also suggests a role for HSP47, a collagen-specific chaperone, in SSc fibrosis by stabilizing procollagen molecules in the endoplasmic reticulum, reinforcing excessive ECM accumulation [96,97]. Finally, targeting pro-inflammatory cytokines such as TWEAK (TNF-like weak inducer of apoptosis), which enhances fibroblast proliferation and monocyte recruitment, may offer novel therapeutic avenues for reducing fibrosis and vascular damage in SSc [98] (Table 1).

3.4. Vascular Modulators in Systemic Sclerosis

Vascular dysfunction is a hallmark of SSc, together with endothelial damage, aberrant angiogenesis, and vasculopathy, which play roles in disease progression. Among the key regulators of vascular homeostasis in SSc are angiopoietin-2 (Ang-2), vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1 (PAI-1). Ang-2, produced by endothelial cells, destabilizes vascular structures, promoting inflammation and fibrosis [99]. Elevated Ang-2 levels correlate with pulmonary arterial hypertension (PAH) severity in SSc patients, suggesting its potential as a biomarker [100]. Decreased Angiopoietin-1 (Ang1) levels and increased Angiopoietin-2 (Ang2) levels have been observed in SSc patients compared with healthy controls, supporting the hypothesis that an imbalance between these molecules contributes to aberrant angiogenesis and microvascular damage [101]. Conversely, VEGF, a crucial pro-angiogenic factor, is paradoxically increased in SSc but fails to compensate for the loss of microvasculature, leading to ineffective angiogenesis [102,103]. PAI-1, a major inhibitor of fibrinolysis, contributes to endothelial dysfunction by promoting pro-coagulant activity, further exacerbating vascular complications [104] (Table 1).

3.5. Oxidative Stress in Systemic Sclerosis

Increased reactive oxygen species (ROS) production by endothelial cells and activated fibroblasts promotes DNA damage, cytokine release, and fibroblast differentiation [105]. Among the most studied oxidative stress mediators in SSc is NADPH oxidase (NOX), particularly NOX4, which is overexpressed in fibroblasts and contributes to TGF-β-driven fibrosis [106]. Additionally, markers of oxidative damage, such as 8-isoprostane and advanced oxidation protein products (AOPP), have been found elevated in SSc [107]. Oxidative stress also impacts endothelial dysfunction by reducing nitric oxide (NO) bioavailability, leading to vasoconstriction and microvascular damage [108]. Antioxidant therapies targeting NOX4 inhibition, mitochondrial dysfunction, and ROS scavengers have shown promise in preclinical models, suggesting that counteracting oxidative stress could slow disease progression [109] (Table 1).

3.6. Hormones in Systemic Sclerosis

Leptin, an adipokine primarily produced by adipocytes, is involved in immune modulation, energy homeostasis, and fibrotic signaling. Elevated serum leptin levels have been observed in SSc patients, correlating with disease severity, pulmonary arterial hypertension (PAH), and skin fibrosis [110,111]. Leptin promotes macrophage activation and T-cell proliferation, leading to a pro-inflammatory environment that amplifies fibroblast activation and extracellular matrix (ECM) deposition in other connective tissue diseases [112]. It has been proposed that adiponectin may mitigate endothelial damage and fibroblast overactivation [113]. Another critical player is gremlin-1, a BMP (bone morphogenetic protein) antagonist that inhibits antifibrotic BMP-4 and BMP-7 signaling, thereby enhancing TGF-β-mediated fibrosis in SSc [114,115]. IGFBP7 (insulin-like growth factor binding protein 7) is another emerging biomarker in SSc, as its elevated levels are associated with fibroblast proliferation, endothelial dysfunction, and pulmonary fibrosis progression [116,117]. Also, IGF-1 (insulin-like growth factor 1) is upregulated in SSc and contributes to fibroblast differentiation and collagen production, further exacerbating fibrosis and inflammation in other models [118]. Studies suggest that targeting leptin, gremlin-1, or IGF-1 pathways could modulate fibrotic signaling with the potential to slow fibrotic progression in other diseases [118] (Table 1).

3.7. Other Modulators in Systemic Sclerosis

Galectin-3, a β-galactoside-binding lectin, has been implicated in immune activation and fibrosis in SSc. Studies have shown that elevated serum galectin-3 levels correlate with cardiac involvement, pulmonary fibrosis, and increased mortality [119,120]. Galectin-3 enhances fibroblast activation, promotes TGF-β signaling, and facilitates myofibroblast differentiation, reinforcing pathological ECM remodeling [121]. Osteopontin (OPN), a glycoprotein involved in cell adhesion and immune regulation, is also upregulated in SSc, driving monocyte recruitment, fibroblast activation, and collagen synthesis [122]. Some studies suggest that elevated OPN levels predict pulmonary arterial hypertension (PAH) and increased mortality in SSc patients [122]. Another emerging biomarker is S100A6 (calcyclin), a calcium-binding protein associated with fibroblast proliferation, inflammatory cell migration, and oxidative stress responses in SSc [123]. FSTL1 (follistatin-like 1), a secreted glycoprotein, has been identified as a potent TGF-β enhancer, exacerbating fibroblast activation and ECM accumulation [124]. In addition, NETosis, a process where neutrophils release extracellular traps (NETs) composed of chromatin and proteases, has been implicated in vascular injury and immune dysregulation in SSc [125]. Excessive NET formation promotes endothelial damage and amplifies the fibrotic response in other models [126]. Finally, LRG1 (leucine-rich alpha-2-glycoprotein 1) is emerging as a key regulator of endothelial dysfunction and fibroblast differentiation, with increased LRG1 levels being associated with other inflammatory vascular complications [127,128] (Table 1).

4. Discussion

Systemic sclerosis (SSc) presents unique challenges that necessitate the search for early biomarkers capable of aiding in diagnosis and predicting specific organ involvement. Defining "early" in this context is complex, as a diagnosis cannot precede clinical manifestations—a long-standing issue in rheumatology. SSc typically progresses through cyclical phases, transitioning from an inflammatory state to a fibrotic one, often within as little as a year. In some cases, these cycles occur only once, while in others, each episode triggers additional organ involvement. While cutaneous manifestations remain a primary diagnostic focus, the early identification of rapidly progressive forms, as well as pulmonary, pulmonary vascular, and fibrotic cardiac involvement, should be prioritized.

Several biomarkers have emerged from studies on pulmonary involvement in SSc. KL-6, cytokines that act as precursors to the inflammatory process, and molecules associated with extracellular matrix deposition and fibrotic activation have been highlighted as potential indicators of progressive and irreversible lung fibrosis in patients with interstitial lung disease (ILD). A crucial question that arises is whether identifying a biomarker that reflects the underlying pathophysiological process is sufficient to provide therapeutic targets for halting disease progression.

Recent literature reinforces the central role of inflammation- and fibrosis-related mediators in systemic sclerosis pathogenesis. Notably, TNF-α has been linked to both fibrotic progression and vascular injury, with elevated levels correlating with pulmonary fibrosis and PAH [129]. The modulation of TNF-α and downstream markers such as VEGF, IL-6, and type I/III collagen fragments through biologic therapy provides further support for their use as dynamic biomarkers. Parallel insights from the EUSTAR cohort highlight how racial background influences autoantibody profiles (ACA, ATA) and pulmonary parameters such as FVC and DLCO, underlining the relevance of stratifying biomarker analysis by patient ancestry [130].

As a research group, we suggest that organizing biomarker interpretation around their molecular function and temporal involvement in disease progression could enhance our ability to predict tissue damage in systemic sclerosis. A plausible strategy may in-

volve first establishing an inflammatory signature at the time of diagnosis, regardless of clinical phenotype. This could then be complemented by the identification of markers reflecting early activation of damage-related pathways in target organs—such as endothelial dysfunction or cardiomyocyte stress—and, finally, by assessing proteins associated with fibrotic commitment or irreversible remodeling. In this framework, incorporating epigenetic biomarkers, including regulatory proteins and non-coding RNAs, may offer an additional layer of insight, helping to define a patient-specific molecular signature at baseline that could inform both prognosis and treatment planning. Furthermore, leveraging multidimensional data analysis, including dimensionality reduction techniques such as principal component analysis (PCA), could enable a more precise reclassification of SSc subtypes at the time of diagnosis. This approach may help identify patients at higher risk of developing severe disease phenotypes or specific organ complications, facilitating personalized therapeutic strategies.

5. Conclusions

In this review, we compiled a comprehensive list of biomarkers with potential involvement in inflammatory, fibrotic pathways observed in SSc. Some of these markers have been validated in animal models, while others have been extensively studied in patient cohorts with defined clinical outcomes. The greatest challenge remains in further investigating and understanding the inflammatory pathways that drive terminal fibrosis and its progression rate, particularly in rapidly progressive skin forms. Identifying reliable and specific biomarkers for these processes could, through the integration of multiple variables, help establish a predictive profile for preventing irreversible tissue damage in SSc patients. Future studies should prioritize multi-omic approaches to better define the temporal dynamics of biomarker expression and their predictive value in disease progression. Ultimately, translating these molecular insights into clinical practice will be essential for developing targeted therapies, improving patient outcomes, and advancing precision medicine in systemic sclerosis.

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