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Systematic Review

The Metabolomic View of Systemic Sclerosis—A Systematic Literature Review

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Abstract: The mortality risk in systemic sclerosis (SSc) is primarily determined by pulmonary involvement (interstitial lung disease (ILD), pulmonary fibrosis), pulmonary arterial hypertension (PAH), and cardiac involvement. With timely and intensive treatment, the disease can be halted or even improved. Therefore, early diagnosis remains crucial. Unfortunately, biomarkers currently available cannot meet this requirement. SSc is characterized by autoimmune inflammation, vasculopathy, and fibrosis. The immunometabolic characterization of autoimmune diseases contributes to a better understanding of the underlying inflammatory processes. In this narrative review, we included 13 studies on metabolomic patterns in SSc in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA). Current studies indicate an altered metabolome in SSc. All documented significant differences between patients with SSc and healthy controls, although the observed metabolomic patterns in SSc were inconsistent between studies. Metabolome alterations include, in particular, energy-related metabolic pathways such as glycolysis/gluconeogenesis, including the synthesis and degradation of ketones, fatty acid oxidation, amino acid-related metabolic pathways, lipid metabolism, and the tricarboxylic acid (TCA) cycle, including pyruvate metabolism. The most frequently examined organ complications with reported significant aberrations of the metabolome were skin involvement, ILD, and PAH. Conclusion: The detailed characterization of the SSc-specific metabolome promises a more comprehensive understanding of the pathogenic mechanisms of the disease. Furthermore, the detection of associations between specific metabolic aberrations and disease phenotypes bears hope for new biomarkers and an improved personalized approach to diagnostics, therapy, and follow-up in the management of SSc.

Keywords: metabolomics; metabolome; systemic sclerosis; biomarkers

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1. Introduction

Systemic sclerosis (SSc) is a life-threatening rheumatic disease characterized by autoimmunity, vasculopathy, and inflammatory fibrosis, which represents an immense burden for patients due to its high morbidity and mortality [1–4]. In addition to a significant impairment in quality of life, the disease burden of SSc exceeds that of other rheumatic diseases [5,6]. A causal therapeutic approach does not exist. SSc is characterized by heterogeneous clinical symptoms, among which interstitial lung disease (ILD) with development

of fibrosis, idiopathic and associated pulmonary arterial hypertension (PAH), and cardiac involvement are prognostically relevant [6]. Of note, these manifestations of systemic sclerosis are often clinically oligo or asymptomatic in the initial phase and develop slowly over time. Therefore, it is standard practice to use comprehensive clinical, radiological, and laboratory analyses to phenotype patients at initial presentation [7,8]. Early and accurate diagnosis of both the underlying disease and emerging organ involvement is crucial. The assessment of the individual disease course, particularly with regard to the prognostically pertinent risk of visceral organ involvement, represents an unsolved burden in daily clinical practice. Apart from the modified Rodnan Skin Score (mRSS), the autoantibody profile, and capillary microscopy [9–11], no biomarkers are routinely used, and individual prognosis remains difficult to estimate [6]. Consequently, there remains an unmet need for new biomarkers to determine disease activity and assess SSc-associated prognosis. With regard to pathogenesis, SSc is increasingly understood as a complex interplay between environmental factors and the development of autoantibodies. In the early active phase of the disease, inflammatory and vasculopathic mechanisms seem to predominate, whereas fibrosing processes become more dominant over time [12]. Furthermore, microvasculopathy with activation of endothelial cells, as well as surrounding perimyocytes and smooth muscle cells, has been observed. Humoral and cellular factors activate aberrant fibroblasts, leading to excessive extracellular matrix production and subsequent fibrosis of the skin and organs [13–17]. Environmental factors appear to modulate the risk of developing SSc [18]. For instance, individual case reports in the 1980s pointed to factors impairing tryptophan metabolism as possible modulators in the pathogenesis of scleroderma-like illness [19]. More recently, changes in the intestinal microbiome (dysbiosis) have been described in SSc [20,21]. Microbial communities play an essential role in host physiology and have profound effects on immune homeostasis and the host metabolome, either directly or via their metabolites and/or components. Thus, metabolomic analyses provide insights beyond metabolic and energy status. For example, metabolites and metabolic pathways influence post-translational modifications [22] of DNA and histones, thereby affecting gene expression [23,24]. Metabolic activities can also regulate apoptosis sensitivity [25,26] and serve as cellular or pathogen-derived RNA-binding proteins [27]. Finally, some metabolites act directly as pro- or anti-inflammatory signaling molecules [28–30]. Most SSc patients clinically show a body composition that differs significantly from healthy controls (HCs) (e.g., muscle function/bone density) [31].

Metabolomics is the comprehensive analytical characterization and large-scale scientific study of small molecules, commonly referred to as metabolites, within an organism, biofluids, cells, or tissues [32,33]. Despite variations in definition, Robert D. Hall defined the metabolome as the entirety of low-molecular-weight products within an organism, with a mass of less than 1500 Da [34]. These metabolites play critical roles in biological systems, acting as intermediates as well as end products of cellular processes, thereby reflecting the biochemical activity and physiological state of the organism. By profiling metabolites, metabolomics offers valuable insights into the underlying mechanisms of health, disease, and environmental interactions [32]. Two of the most powerful analytical techniques in metabolomics are mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. Mass spectrometry is characterized by its high sensitivity and selectivity. Furthermore, it can be coupled with various chromatographic separation systems, such as liquid chromatography (LC), gas chromatography (GC), and capillary electrophoresis (CE). These combinations reduce ion suppression, separate isobaric compounds, minimize the signal-to-noise ratio, and ultimately improve detection limits and spectrum complexity. Most commonly, LC and GC couplings with high-resolution mass spectrometry are used in metabolomic research. LC separates complex mixtures of metabolites based on their

chemical properties, such as polarity and hydrophobicity, using a liquid mobile phase. Gas chromatography, by contrast, utilizes a gaseous mobile phase and is suited for volatile compounds. The mass spectrometer identifies and quantifies compounds by measuring their mass-to-charge (m/z) ratio. However, mass spectrometry has limitations, including the often extensive sample preparation, the complexity of processing large datasets, and notably, reduced reproducibility. NMR spectroscopy, on the other hand, offers a non-destructive approach to metabolomics by exploiting the magnetic properties of atomic nuclei. NMR provides highly reproducible and quantitative data, along with structural information about metabolites. Its ability to analyze complex mixtures without extensive sample preparation makes it a valuable tool in metabolomics. Nonetheless, the technique has disadvantages, such as lower sensitivity compared to MS. Signal overlap in complex NMR spectra, compounded by limited coupling possibilities, restricts the number of detectable and quantifiable metabolites [35,36]. In summary, the comprehensive analysis of the metabolome is challenged by its diversity and dynamic nature. MS and NMR are complementary techniques, each offering unique advantages for elucidating the intricate network of metabolites. Their integration is facilitating deeper biological insights and biomarker discovery [36].

Consequently, metabolomic analyses in SSc offer promising opportunities to expand our knowledge of pathogenesis, SSc-specific immunometabolism, phenotyping, prognostic characterization, and risk stratification.

2. Methods and Search Strategy

A systematic review of all papers published in English on the topic of metabolome analyses in systemic sclerosis was carried out using the databases PubMed, Scopus, and Web of Science in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA) [37] (Figure 1). The search terms/keywords used were (“metabolome”) AND (“systemic sclerosis”), (“metabolome”) AND (“scleroderma”), (“chromatography–mass spectrometry”) AND (“systemic sclerosis”), (“chromatography–mass spectrometry”) AND (“scleroderma”), (“NMR”) AND (“systemic sclerosis”), (“NMR”) AND (“scleroderma”). The time span of the publications was 2015–2025. The time of the systematic literature search was December 2024. Titles and abstracts were first reviewed for topical relevance, followed by a full-text review by the authors independently to ensure only articles that met the predefined inclusion and exclusion criteria were included. Our protocol is registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) under doi: 10.37766/inplasy2025.5.0077.

Inclusion criteria:

- Original research articles (cohort, case control studies), addressing the human, adult serum or plasma metabolome in SSc, published without restriction to a single metabolite and published in English within the last ten years.
- Use of HPLC/UPLC-MS or LC-MS or 1H-NMR.
- SSc diagnosis according to the 2013 American College of Rheumatology and European League Against Rheumatism ACR/EULAR classification criteria.

The exclusion criteria were defined as follows:

- Studies focusing on other biological samples, e.g., urine.
- In vitro studies.

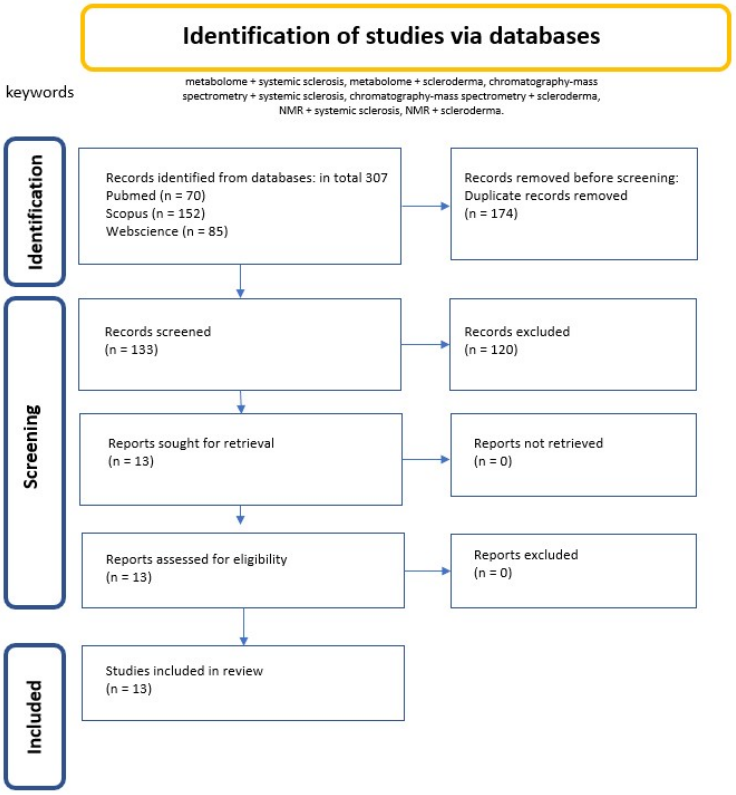


Figure 1. PRISMA 2020 flow diagram according to [37].

3. Results

A total of 307 papers were found. After applying the criteria described above, 13 papers were selected that met our criteria.

3.1. Serum or Plasma Metabolome in Systemic Sclerosis

A total of 17 studies on the serum or plasma metabolome in systemic sclerosis were identified that met the predefined inclusion criteria. Two of these studies did not primarily focus on SSc but either looked at connective tissue diseases in general [38] or analyzed the metabolome in systemic lupus erythematosus (SLE) and used SSc as a control group [39]. The number of SSc patients included in the individual studies varied between 19 and 206. The work of Xie et al. [40], which carried out a meta-analysis based on genome-wide association study (GWAS) data for plasma metabolites (taken from the GWAS catalog (GCST90199621-GCST90204603)) and included a total of 26,679 people (9095 SSc patients and 17,584 healthy controls), should be considered separately at this point. The individuals in this study came from 14 European–American SSc GWAS cohorts from a total of 10 countries. The plasma metabolite data included 1091 blood metabolites and 309 metabolite ratios. The majority of the studies report the serological status and clinical presentation, such as the limited and diffuse cutaneous form of SSc (lcSSc/dcSSc) of the patients. In our selected studies for review, nine studies used plasma and eight studies used serum for the analysis. Where healthy subjects were included as controls, significant differences between the metabolome of SSc and HCs were found. Eleven studies reported specific metabolomic fingerprints with respect to clinical subtype or organ involvement. One study postulated causal effects of specific gut microbiota and plasma metabolites on the development of SSc [40]. In the following, the study results on specific metabolome profiles or altered metabolome pathways will be presented from a clinical perspective, sorted according to the categories (I.) skin manifestations, (II.) interstitial lung disease/fibrosis, (III.) pulmonary arterial hypertension (PAH), and (IV.) disease prognosis or treatment response.

3.2. Skin Manifestation

Several metabolite changes were described in association with cutaneous manifestations in SSc, identifying both parameters with positive and negative correlation to skin fibrosis. Guo et al. [41] demonstrated a negative correlation between allysine and all-trans-retinoic acid (which also correlated with inflammatory parameters). Markers that correlated positively with mRSS in this study population were D-glucuronic acid and hexanoylcarnitine. Furthermore, sclerodactyly was negatively associated with thromboxane B2 and positively associated with phthalic acid.

In vitro background data support the role of amino acids in the immunometabolism of skin fibrosis in SSc, while increased collagen synthesis appears to be a concomitant symptom of cutaneous fibrosis. Interestingly, Ung et al. demonstrated an upregulation of amino acid metabolites such as glutamine, ornithine, proline, and citrulline, which are involved in collagen metabolism [42]. It is known that proline is required for collagen production and the synthesis of the extracellular matrix [43]. Proline is also present in increased amounts in fibroblasts stimulated with transforming growth factor beta (TGF-β) [44]. Glutamine, in turn, promotes proline synthesis and supports collagen production in fibroblasts [45]. With regard to glutamate metabolism, it has been shown that under the influence of TGF-β1, myofibroblasts have increased glutamate levels, while glutamine levels decrease, indicating accelerated glutaminolysis. Glutaminolysis is considered to be one of the main energy sources for effector T cells and facilitates the pro-inflammatory Th17 phenotype [46]. Smoleńska et al. [47] specifically investigated the amino acid metabolome in SSc, showing correlations between amino acids and their derivatives and clinical skin manifestations. In the diffuse cutaneous subtype (dcSSc), increased concentrations of sarcosine, β-alanine, methylnicotinamide (MNA), and L-NAME (N-nitroarginine methyl ester) were detectable. Calcinosis correlated positively with sarcosine, glutamate, proline, tyrosine, 3-methylhistidine, and ornithine levels. The extent of skin fibrosis measured by mRSS showed a negative correlation with sarcosine, proline, histidine, ornithine, asparagine, citrulline, and phenylalanine. L-NAME, glutamate, and lysine were associated with the increased occurrence of telangiectasias. This study revealed changes in amino acid metabolism, which could represent a link to SSc-associated vasculopathy. An increase in asymmetric dimethylarginine (ADMA) was detected. ADMA is an inhibitor of NO synthase, which supports the assumption of endothelial damage as the etiology of SSc.

However, besides alterations in amino acid pattern in the context of skin fibrosis in SSc, changes in lipid metabolism have also been observed. Recently, growing evidence suggests that changes in lipid metabolism could have a general influence on the modulation of fibrosis, immunity, and angiopathy in SSc [48]. Sphingomyelins were detected in reduced concentrations, which correlated with greater skin involvement [49]. Some metabolites of sphingomyelin, such as sphingosine 1-phosphate, regulate immune cell chemotaxis, vascular dilation, and angiogenesis via G protein-coupled receptors. Stimulation of lymphocytes, monocytes, and fibroblasts by sphingosine 1-phosphate has been described [50], which could establish a connection to inflammatory skin fibrosis. Furthermore, a correlation between specific lipoproteins and the severity of skin fibrosis was described in a study that simultaneously identified a specific lipoprotein pattern in SSc-ILD [51]. Jendrek et al. were able to retrace a negative correlation of high-density lipoprotein (HDL) and (apolipoprotein (Apo) A1/A2 levels with skin fibrosis measured by mRSS as a validated clinical endpoint in SSc [9].

3.3. Focus on Interstitial Lung Involvement (ILD) and Pulmonary Fibrosis

Visceral organ manifestations—especially interstitial lung disease with pulmonary fibrosis, cardiac involvement, and pulmonary arterial hypertension—significantly determine SSc-associated lethality [6]. Therefore, new prognostic and personalized biomarkers

are urgently needed. Dyslipoproteinemia and alterations in the lipid profile are frequently present in SSc patients [52]. Lipids serve various functions, including acting as signaling substances for the immune system. Lipid subgroups such as short-chain fatty acids (SCFA) also appear to influence the differentiation of T lymphocytes by modulating histone deacetylase activity [53]. For example, supplementation of SCFA butyrate has demonstrated anti-inflammatory effects in chronic inflammatory bowel disease [54]. Comparable effects in SSc have not yet been investigated. However, butyrate levels are also found to be reduced in individuals with SSc [55,56].

With regard to ILD, the work of Guo et al. [41] provides a comprehensive metabolic fingerprint. This analysis included 127 non-treated (59.8% female) and 57 treated (59.6% female) individuals. Serum samples were analyzed using LC-MS. Parameters positively associated with ILD were γ-linolenic acid, dihydrothymine, etiocholanol glucuronide, L-pipecolic acid, carnosine, and L-cystathione. A negative association with the ILD diagnosis existed for the parameters proline, betaine, androsterone sulfate, phloretin-2′-O-glucuronide, 4-guanidinobutanoic acid, and NNAL-N-glucuronide (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol-N-glucuronide). Notably, the study also described a negative correlation between L-tryptophan and inflammatory markers.

However, studies focusing on the metabolic signature of SSc-ILD have yielded inconsistent results. For example, Belocchi et al. [57] were unable to demonstrate any metabolomic difference between patients with and without ILD. However, metabolic differences were detected between SSc and HC in this study. Diacylglycerol 38:5, phosphatidylcholine 36:4, 1-(9Z-pentadecenoyl)-glycero-3-phosphate, DL-2-aminooctanoic acid, 2,4-dinitrobenzenesulfonic acid, and α-N-phenylacetyl-L-glutamine differed significantly from HC. 59 SSc individuals (88.1% female, 17.1% dcSSc, 39% ACA positive, 39% anti-scl70 positive) were included and analyzed using LC-MS plasma analysis. Special attention was paid to intestinal involvement and microbiota disturbances. Therefore, the authors found that intestinal microbiota analysis could also distinguish SSc patients from HC (reduced prevalence of nine bacterial species from Firmicutes, Bacteroidetes, and Proteobacteria families). In general, it is accepted that this dysbiosis can lead to reduced butyrate production. Bögl et al. [58] provided metabolic evidence of intestinal microbiome dysregulation, although no significant association with ILD was observed. This work primarily identified amino acids (dimethylarginine, citrulline, ornithine, 1-methylhistidine, taurine, 3-methylhistidine, tryptophan, alanine, tyrosine, methionine, lysine, proline), their derivatives, and other metabolites (kynurenine, TMAO, trimethyllysine, hexanoylcarnitine, acetylcarnitine, choline, octanoylcarnitine, valerylcarnitine) as dysregulated in SSc.

However, another study by Meier et al. [59], which focused on SSc-ILD, was able to identify a distinct metabolomic profile in SSc-ILD. This study involved a smaller cohort of 36 SSc individuals (83.3% female, 25% dSSc, 33.3% ACA positive, 27.8% anti-Scl70 positive), analyzed using targeted LC-MS (110 molecules) from serum samples. Differences were shown between non-ILD-SSc, stable ILD-SSc, and progressive ILD-SSc. Remarkably, 85 distinct substances were identified, including various amino acid metabolites. Concentrations of L-threonine, xanthosine, 3-aminoisobutyric acid, leucine, isoleucine, and adenosine monophosphate were associated with ILD and correlated with a deterioration in lung function tests. L-tyrosine, leucine, isoleucine, and L-tryptophan were discussed as potential SSc-ILD biomarkers. Additional SSc-ILD biomarkers (L-glutamine and Ile-Ala) were identified by Sun et al. [60], performing untargeted LC-MS of serum in a cohort of 30 SSc individuals (80% female, 40% dcSSc). They found 38 compounds at different concentrations, 32 of which demonstrated good diagnostic value (including vitamin E, various lipid metabolites, and amino acids). In addition, different patterns were observed for cutaneous subtypes (dcSSc and lcSSc).

Our own group [51] showed that patients with SSc-ILD and lung fibrosis display reduced HDL levels. Furthermore, a reduction in ApoA1 + A2 and its HDL fractions reflected a distinct lipoprotein profile for SSc-ILD patients, independent of potential clinical confounders for dyslipidemia. Notably, SSc-ILD HDL levels correlate with FVC (forced vital capacity), DLCO (diffusion capacity of the lungs for carbon monoxide), and mRSS. These results suggest that HDL and its subfractions may be considered as potential new biomarkers for SSc-ILD. The correlation with severity of lung involvement, measured by FVC and DLCO, as well as the independent correlation with mRSS, underlined the relevance of HDL and lipoprotein profiling in SSc-ILD.

Further evidence of pathological lipid metabolism in SSc was provided by Ottria et al. [61]. This study included a discovery cohort with 20 SSc individuals (85% female, 35% dcSSc, 55% ACA positive, 25% anti-scl70 positive) and a validation cohort with 12 SSc individuals (92% female, 16.7% dcSSc, 25% ACA positive, 50% anti-scl70 positive). In the discovery group, LC-MS was used, and in the validation group, GC-MS (for carnitine) and a fatty acid analysis (via LC-MS) in plasma were performed. Using untargeted LC-MS analysis, 46 metabolites that differed from HC were initially detected, indicating impaired fatty acid oxidation and renal dysfunction in the SSc. The targeted analysis focusing on fatty acids and carnitine concentrations identified significant differences in the concentrations of lauric acid, myristic acid, arachidic acid, carnitine, isovalerylcarnitine, octanoylcarnitine, and palmitoylcarnitine. In addition, in a functional assay, inhibition of carnitine transporters in dendritic cells from patients with SSc suppressed pro-inflammatory reactions. Therefore, the authors discuss L-carnitine and acylcarnitines as potential biomarkers for SSc.

A different metabolome signature of SSc-ILD vs. SSc patients without ILD was also shown in the work of Fernández-Ochoa et al. [49]. The authors compared the lcSSc and dcSSc groups but found no significant plasma differences between SSc-ILD and SSc-nonILD. However, in urine samples, deregulated metabolites were acylcarnitines, acylglycines, and again metabolites derived from amino acids, especially proline, histidine, and glutamine, which could become biomarkers for SSc-ILD. 2-arachidonoylglycerol, which is upregulated in SSc compared to HC, was also discussed as a possible biomarker given its role in the endocannabinoid system and possible involvement in SSc-associated autoimmunity.

In a subsequent study [38], Fernández-Ochoa et al. presented that urine analysis can achieve greater accuracy in the differentiation of SSc from mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD), as well as rheumatoid arthritis or systemic lupus erythematosus. Unfortunately, the authors did not provide any information on specific deviations in SSc within this cohort.

3.4. Focus on Pulmonary Arterial Hypertension (SSc-PAH)

Pulmonary arterial hypertension (PAH) is characterized by damage to the smaller arteries in the precapillary circulation of the pulmonary vessels and occurs with an average frequency of about 9% (5–15%) in SSc. However, it is one of the main causes of death in SSc [62,63]. PAH can occur as a primary condition or develop as a consequence of SSc-ILD. Early diagnosis is important, as studies have shown that early therapeutic intervention can improve survival rates [64]. Since some PAH-specific therapeutics mediate their effect by modulating intracellular endothelial metabolism, investigating immunometabolic changes in SSc-PAH is relevant.

Two studies compared metabolomic patterns between SSc patients with PAH and SSc patients without PAH [56,65]. Another study [66] also included idiopathic pulmonary arterial hypertension (IPAH) as a disease control. Deidda et al. [56] initially reported that patients with SSc-PAH showed higher levels of carboxylic acids (e.g., lactate) and lipoproteins, while amino acid levels, especially L-arginine, were reduced compared to patients with SSc without PAH. The study used NMR spectroscopy, directly analyzing pulmonary artery

blood. In detail, SSc-PAH patients had increased concentrations of acetoacetic ester, alanine, lactate, VLDL and LDL levels, and decreased γ-aminobutyric acid, arginine, betaine, choline, creatine/creatinine, glucose, glutamate/glutamine, glycine, histidine, phenylalanine, and tyrosine levels. In addition, significantly higher ADMA levels and reduced L-arginine levels were documented in SSc-PAH compared to non-PAH patients [65]. In this study, serum ADMA levels $\geq$ 0.7 µM were also discussed as a diagnostic biomarker with a sensitivity of 86.7% and a specificity of 90.0% for PAH [65]. The work of Alotaibi et al. [66], including a disease control group, analyzed plasma from SSc patients with and without PAH as well as from patients with IPAH. They found nine metabolites characteristic of SSc-PAH (lignoceric acid, nervonic acid, fatty acid esters of hydroxy fatty acids, nitrooleate, 11-testosterone, 17β-estradiol, new eicosanoid, prostaglandin F2α, leukotriene B4). Among these, several parameters seemed to correlate with the severity of SSc-PAH. In this study, it was also noted that lignoceric acid and leukotriene B4 are present in higher concentrations in SSc without pulmonary hypertension. Overall, the above observations support the hypothesis of a dysregulated metabolism of fatty acids, steroid hormones, and arachidonic acid. Another study [67] demonstrated that dysregulation of the kynurenine pathway could serve as a predictor for the development of SSc-PAH. However, a correlation with other manifestations of SSc-associated microvasculopathy, such as Raynaud's syndrome or the occurrence of telangiectasias, could not be established in this cohort.

3.5. Focus on Further Prognostic Metabolome Signatures Including Treatment Response:

The heterogeneous disease manifestations of SSc with their variable and unpredictable courses justify the urgent need for diagnostic, personalized, and prognostic biomarkers. However, only a few studies provide information on treatment response, primarily due to limitations in the study design and small cohort sizes. However, the analysis of the metabolome can offer, e.g., prognostic information about the cutaneous disease severity. The most important metabolic pathways that were altered in dcSSc compared to lcSSc included glycolysis and gluconeogenesis as well as glutamate-glutamine metabolism [55]. The previously mentioned study by Guo et al. [41] not only analyzed the correlation of metabolomic parameters with mRSS but also examined metabolic changes in response to therapy-induced regression of skin involvement. They found that some of the deviating metabolites (γ-carboxyethylhydroxychroman (γ-CEHC), paraxanthine, PS(18:0/18:1(9z)), 2,3-diaminosalicylic acid, MG(0:0/182(9Z,12Z)/0:0), and phloretin-2′-O-glucuronide) normalized during treatment in the SSc group, suggesting their potential as biomarkers for cutaneous treatment response. Additional parameters, such as mediagenic acid-3-O-β-D-glucuronide, 4′-O-methyl-(-)-epicatechin-3′-O-β-glucuronide, and valproic acid glucuronide, were identified, although no causal relationship was established. Prognostic factors for SSc-ILD were considered in the study by Meier et al. [59]. The colleagues were able to distinguish progressive SSc-ILD from stable SSc-ILD based on several metabolome changes. This study showed that the levels of L-leucine and L-isoleucine were highest in HC and gradually decreased from SSc patients without ILD to those with stable ILD. In addition, L-tryptophan, L-tyrosine, L-threonine, and adenosine monophosphate showed a similar decline, while 3-aminoisobutyric acid and 1-methyladenosine showed an inverse trend. Based on this study, the determination of branched chain amino acids (BCAA: L-leucine and L-isoleucine) was discussed as prognostic biomarkers for the course of SSc-ILD. BCAA levels also correlated significantly with disease activity. In a separate BCAA assay, a cut-off value of 250.3 µM was defined for the differentiation of stable ILD from progressive ILD [59]. These results were confirmed by analysis of a validation cohort.

Table 1 presents a summary, including the characteristics of the groups ex-amined in the studies, as well as the techniques used and selected key findings of the pa-pers.

Table 1. Overview of the original articles included in this review, with the methods used and a selection of the specific key findings. Abbreviations: IPAH (idiopathic pulmonary arterial hypertension); ACA (anti-centromere antibodies); dcSSc (diffuse systemic sclerosis); HC (healthy controls); ILD (interstitial lung disease); mRSS (modified Rodnan skin score); SLE (systemic lupus erythematosus); SSc (systemic sclerosis); L-NAME (N-nitroarginine methyl ester); FVC (forced vital capacity); DLCO (diffusion capacity of the lungs for carbon monoxide); pulmonary arterial hypertension (PAH).

Original Papers	Cohort/Control	Analytical Technique, Method	Result Selection
Fernández-Ochoa Á et al., 2020 [38]	N = 43 SSc (83.6% female)/HC	liquid chromatography–mass spectrometry (LC-MS), plasma and urine analysis	Differences in L-kynurenine and N-acetylaspartylglutamic acid compared to controls. No further characterization of SSc individuals. Focus on other autoimmune diseases. Urine metabolites can tendentially achieve better accuracy.
Bengtsson AA et al., 2016 [39]	N = 19 SSc (84% female, 52.6% dcSSc, 42.1% ACA positive, 21%, anti-Scl70 positive)	gas chromatography–mass spectroscopy (GC-MS)	Focus on SLE, SSc individuals served as control, e.g., increase in arginine and simultaneous decrease in 2-oxoglutaric acid for SSc compared to HC and SLE.
Guo M et al., 2023 [41]	N = 127 SSc non-treated (59.8% female, 57 treated (59.6% female)	high-performance liquid chromatography–quadrupole-time-of-flight mass spectrometry (HPLC-Q-TOFMS)/MS	Starch and sucrose metabolism, proline metabolism, androgen and estrogen metabolism, and tryptophan metabolism dysregulated in new-onset SSc, but restored upon treatment. Allysine and all-trans-retinoic acid negatively correlated, while D-glucuronic acid and hexanoyl carnitine positively correlated with mRSS. Proline betaine, phloretin 2′-Oglucuronide, gamma-linolenic acid, and L-cystathionine associated with SSc-ILD.
Smolenska Z et al., 2020 [47]	N = 42 SSc (83.3% female, 50% dcSSc)	liquid chromatography–mass spectrometry (LC-MS)	Increase in concentrations of NO synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA) in SSc vs. HC. NOS inhibitor L-NAME elevated in patients with dcSSc or telangiectasia.
Fernández-Ochoa Á et al., 2019 [49]	N = 59 SSc (88.1% female, 16.9% dcSSc, 39% ACA positive, 39% anti-Scl70 positive)/HC	reversed-phase high-performance liquid chromatography coupled to electrospray ionization-quadrupole-time-of-flight mass spectrometry (RP-HPLC–ESI-Q-TOF-MS)	Main parameters in urine were acylcarnitines, acylglycines and metabolites derived from amino acids (proline, histidine, and glutamine). Main plasma biomarker was 2-arachidonoylglycerol (potential crosslink to endocannabinoid system).

Table 1. *Cont.*

Original Papers	Cohort/Control	Analytical Technique, Method	Result Selection
Jendrek ST et al., 2024 [51]	N = 100 SSc (75% female, 38% dcSSc, 62% lcSSc, 31% SSc-ILD)/HC	proton nuclear magnetic resonance spectroscopy (1H-NMR)	Reduced HDL levels are linked to SSc-ILD independently from clinical confounders. High-density lipoprotein (HDL) and (HDL) apolipoprotein (Apo) A1/A2 levels positively correlate with parameters of lung involvement in SSc-ILD such as FVC and DLCO. HDL and (HDL) ApoA1/A2 levels negatively correlate with skin fibrosis in SSc patients with and without ILD.
Bellocchi C et al., 2018 [57]	N = 59 SSc (88.1% female, 17.1% dcSSc, 39% ACA-positive, 39% anti-scl70 positive)/HC	high-performance liquid chromatography–mass spectrometry (HPLC-MS); 16S rRNA gene amplification and sequencing (fecal microbiota)	Metabolomic alterations in glycerophospholipidmetabolites and benzene derivatives. Microbial and metabolic data showed significant interactions between Desulfovibrio and alpha-N-phenylacetyl-l-glutamine and 2,4-dinitrobenzenesulfonic acid.
Bögl T et al., 2022 [58]	N = 52 SSc (84.6% female, 21.2% dcSSc, 34.6% ACA positive, 32.7 anti-Scl70 positive)/HC [Exclusion criteria for control group: acute infections, liver and/or kidney diseases and diabetes]	high-performance liquid chromatography–mass spectrometry (HPLC-MS)	SSc-specific alterations, inter alia, in the kynurenine pathway, the urea cycle, lipid metabolism.
Meier C et al., 2020 [59]	N = 36 SSc (83.3% female, 25% dSSc, 33.3% ACA positive, 27.8% anti-Scl70 positive)/HC	targeted liquid chromatography–mass spectrometry (LC-MS)	SSc/HC-discriminating profile consisting of 4 amino acids and 3 purine metabolites (L-tyrosine, L-tryptophan, and 1-methyl-adenosine). Differentiation between progressing and stable SSc-ILD through L-leucine, L-isoleucine, xanthosine, and adenosine monophosphate. L-leucine and xanthosine negatively correlated with changes in FVC% and xanthosine negatively correlated with changes in DLCO%.
Sun C et al., 2023 [60]	N = 30 SSc (80% female, 40% dcSSc)	ultra-high-pressure liquid chromatography–quadrupole-time-of-fight mass spectrometry (UPLC-Q-TOF)	Fatty acids, amino acids, and glycerophospholipids, primarily altered in SSc patients. Glutamine metabolism primarily altered in SSc-ILD, whereas amino acid metabolism and steroid hormone biosynthesis primarily altered in leading skin fibrosis.

Table 1. *Cont.*

Original Papers	Cohort/Control	Analytical Technique, Method	Result Selection
Thakkar V et al., 2016 [65]	Case–Control study: 15 consecutive treatment naive patients with newly diagnosed SSc-PAH and compared with 30 SSc-controls without PAH.	high-performance liquid chromatography–mass spectrometry (HPLC-MS);	Asymmetric dimethylarginine (ADMA) levels higher in SSc-PAH.
Alotaibi M et al., 2023 [66]	N = 400 SSc-PAH. Controls: N = 1.082 IPAH. Validation Cohort of 100 patients with SSc without PAH	liquid chromatography–high-resolution mass spectrometry (LC-MS)	Lignoceric acid and nervonic acid, eicosanoids/oxylipins and sex hormone metabolites distinguishing between SSc-PAH and IPAH.
Simpson CE et al., 2023 [67]	N = 62 SSc-PAH, N = 19 SSc comparators without PAH, N = 85 HC	liquid chromatography–mass spectrometry (LC-MS)	Kynurenine and its ratio to tryptophan (kyn/trp) increased over the surveillance period in patients with SSc who developed PAH.

4. Discussion

According to our defined inclusion and exclusion criteria, we identified 13 articles in this review focusing on serum or plasma metabolites in SSc patients and summarized the key findings on dysregulated metabolic pathways in SSc (Table 1).

Only two studies included cohorts of more than 100 individuals [41,51]. Almost all studies compared SSc-associated metabolome changes with healthy controls (HC). Exceptions included one study that focused on SSc-PAH and also included idiopathic pulmonary arterial hypertension (IPAH) as a control [66] and another study that considered other inflammatory rheumatic diseases, using SSc only as a control [38]. In this latter study, SSc individuals were phenotyped in a more restricted manner. Thus, metabolome-phenotype associations must be evaluated with caution in this study. The most frequently examined organ complications with reported significant aberrations of the metabolome were skin involvement, ILD, and PAH. Regarding other organ involvements, no consistent or significant associations with metabolome alterations have been identified in the studies to date. This lack of findings may be attributed to the heterogeneity of SSc manifestations and the often small cohort sizes. One study even found no significant changes in metabolome parameters comparing SSc patients with and without ILD. Furthermore, it remains unclear whether the observed metabolome aberrations are causal or a consequence of SSc.

It should also be noted that the studies that focused on the metabolome pattern in SSc-PAH examined blood from the pulmonary arteries. Consequently, comparability with other studies using peripheral blood as a sample source is limited.

Although the metabolome parameters associated with specific organ manifestations differed between studies, all authors consistently identified significant differences between SSc and HC. However, common disturbed metabolic pathways emerged across studies, particularly including energy-related metabolic pathways such as glycolysis/gluconeogenesis, the synthesis and degradation of ketones, fatty acid oxidation, amino acid-related metabolic pathways, lipid metabolism, and the TCA cycle with pyruvate metabolism. Given the complexity of metabolic profiles, we would like to present selected patterns below and discuss possible implications for SSc pathology. Interestingly, in individual cases [41], previously identified metabolomic abnormalities normalized during treatment, thus warranting further investigation into metabolome–immune phenotype associations. This also implies that, in addition to SSc organ involvement, treatment status and inflammatory activity should always be documented during sample collection in future metabolomic studies and that prospective approaches remain complementary.

Alterations in amino acid metabolism [41,42,56,58,59,65] have been frequently observed in SSc patients, possibly related to protein synthesis and catabolism. In addition to the aforementioned discussed role of specific amino acid metabolites in collagen metabolism and fibrosis development [42–45] and the potential pro-inflammatory Th17 shift through dominant glutaminolysis [46], further metabolome changes in SSc should be discussed in light of the energy metabolism of respective immune effector cells or target cells of autoimmune inflammation, SSc-associated vasculopathy and fibrosis. Referring to the observations of Murgia et al., differentiating cutaneous disease severity based on metabolic changes within glycolysis/gluconeogenesis and glutamate-glutamine metabolism, the respective energy source of immune effector cells may even be a contributing factor. In addition to glucose, amino acids play an important role for T cells as a primary energy source and as a substrate for protein and nucleic acid biosynthesis [68]. Notably, T cells possess a functional GABAergic system that is involved in modulating immune response [69]. Glutamate, a precursor of γ-aminobutyric acid (GABA), acts as an antioxidant through its immediate precursor glutathione [70,71]. Interestingly, glutamine, but not glutamate, uptake is enhanced during T cell activation [72,73], which could explain the observed relative

increase in glutamate and decrease in glutamine in patients with dcSSc compared to lcSSc patients. Glutamine is not only important for protein synthesis but also contributes to other processes, which are important for T cell proliferation, including fatty acid synthesis and the synthesis of purine and pyrimidine nucleotides.

On the other hand, certain amino acid metabolites can facilitate a pro-inflammatory and pro-fibrotic environment, reinforcing the potential causal role of metabolomic changes. For example, BCAAs, particularly leucine and isoleucine, demonstrated prognostic value for the course of SSc-ILD and lung function parameters. Furthermore, especially L-leucine, stimulates protein synthesis and reduces protein degradation through the phosphorylation of mTOR [74]. mTOR plays an important role in anabolic processes by inducing cells to switch from oxidative phosphorylation to aerobic glycolysis [75], while its activity is increased in SSc and pulmonary fibrosis [76]. Another consistent finding across multiple studies is the tendency of SSc patients to lower tryptophan levels [41,58,59]. Possible explanations include enhanced metabolism of this essential amino acid, especially under inflammatory conditions, via the kynurenine-, serotonin-, and indole-3-pyruvate pathways [77]. The majority of tryptophan is metabolized via the kynurenine pathway, which is stimulated by pro-inflammatory substances such as lipopolysaccharides, tumor necrosis factor α, and interleukin 1 and 2 [78]. The resulting kynurenine stimulates CD4 and CD8 double-negative T lymphocytes and thus maintains the inflammatory process [79]. As already mentioned, disturbances in the kynurenine pathway appear to represent a common metabolomic marker for ILD and PAH [58,59,67]. These findings could point towards new avenues for treatment.

In addition to amino acids, several studies have identified a dyslipidemia in patients with SSc, correlating with specific organ manifestations and disease activity. Lipids fulfill multiple physiological functions, for example, acting as structural components of cellular membranes and as an energy source. Furthermore, lipids such as short-chain, medium-chain, and long-chain fatty acids influence immune response, particularly through T-lymphocyte differentiation [53]. Medium-chain fatty acids promote a Th1 and Th17 shift and inhibit Treg cells [80], while (long-chain) fatty acids represent the basis for the production of pro- and anti-inflammatory cytokines [81]. The importance of eicosanoids and other fatty acid derivatives in SSc has already been extensively investigated [48]. However, a detailed discussion is beyond the scope of this article.

Nevertheless, recent findings on changes in lipoprotein subfractions in SSc should be discussed in more detail [51]. A large study with more than 100 SSc patients demonstrated that SSc-ILD is characterized by a dyslipidemic profile. In this study, reduced HDL levels (measured by 1H NMR spectroscopy) were not only associated with SSc-ILD, but additionally, HDL and ApoA1/A2 levels were positively correlated with established parameters of disease severity in SSc-ILD, such as FVC and DLCO. Furthermore, a negative correlation between HDL and its apolipoproteins and skin fibrosis (measured by mRSS) and thus, another validated biomarker was observed [51]. Since these results persisted even after adjustment and multivariate analysis for typical confounding factors of HDL/LDL-dyslipidemia, the often neglected immunological effects of HDL may be discussed as a cause and link to SSc-microvasculopathy. Various immunomodulatory HDL effects have been described: inter alia, anti-apoptotic, anti-inflammatory, endothelial cell repair, and proliferation-enhancing effects. These effects are partly explained by downregulation of the expression of cell adhesion molecules, namely VCAM-1 and ICAM-1, and reduced expression of MCP-1 [82–86]. In this context, the distinct metabolomic profile of endothelial cells in SSc patients with PAH described by Deidda et al. [56], as well as the association of reduced HDL levels in SSc-PAH patients described by Borba et al. [87], should also

be discussed. In addition, another group demonstrated a correlation between cholesterol efflux capacity and skin fibrosis [88].

Conclusively, it is reasonable to speculate that high-resolution metabolomic determination of the lipoprotein profile is suitable for a more individualized assessment of SSc-ILD. Nevertheless, several inherent limitations remain to be considered when applying and interpreting metabolomic analyses. For example, the comparability of studies using different analytical techniques is challenging. In this instance, MS and NMR profiling are widely used techniques for metabolome analysis, each with its own advantages and disadvantages. NMR spectroscopy is robust and reproducible. The sample preparation is relatively simple, and the measurement is non-destructive. However, compared to mass spectrometry, the detection limit is significantly lower. Mass spectrometry is sensitive and can simultaneously analyze a wide range of components. The complexity of the data makes the evaluation process intricate. Despite the promising potential of metabolomics to uncover novel biomarkers and pathophysiological mechanisms in SSc, some further methodological challenges could limit the robustness and reproducibility of current findings. A critical issue is the frequent mismatch between small sample sizes and the high dimensionality of metabolomic data, which increases the risk of overfitting and compromises the stability of feature selection [89]. In this context, it is important to note that of the 13 studies included in this review, 10 included fewer than 100 SSc individuals. Among the studies with fewer than 100 SSc individuals, six studies examined cohorts under 50 individuals (Table 1). Balanced and representative patient stratification with regard to disease activity/stage, (clinical/serological) phenotypes, and demographic characteristics such as age, gender, and ethnicity is, therefore, often lacking. However, since all of these factors can influence metabolite activities, future studies on potential metabolomic biomarkers should include careful patient characterization based on, inter alia, a combination of clinical, biochemical, and radiological profiling. In addition, stratification according to prevalent comorbidities such as sarcopenia, pulmonary cachexia, or chronic kidney disease is also desirable to exclude further metabolomic confounders.

With regard to biomarker studies, it remains necessary to conduct further longitudinal and comparative analyses on different disease phenotypes during disease progression using the same analytical techniques, since different clinical presentations manifest at the onset and during disease progression. In addition to considering age- and sex-matched healthy controls, the inclusion of disease controls in multicenter cohorts in future studies must be postulated in order to be able to specify potential biomarkers.

Furthermore, batch effects introduced during sample processing and data acquisition can confound biological signals if not adequately controlled [90]. Biological variability, stemming from disease heterogeneity, comorbidities, medication use, and lifestyle factors, adds another layer of complexity, often obscuring disease-specific metabolic signatures [91,92]. Compounding these issues is the limited availability of external validation cohorts, which limits the generalizability of proposed biomarkers.

Addressing these challenges requires rigorous study design, standardized protocols, appropriate statistical frameworks, and multicenter collaborations to enable robust validation in future large-scale cohort studies on SSc-associated metabolomics. Characteristic and clinically challenging features of SSc remain the great heterogeneity of clinical manifestations and the high variability of disease progression in individual patients. In this regard, disease-specific biomarkers can have different functions. They may be used for diagnosis, monitoring of therapy, or for prognosis.

In terms of (early) diagnostic utility, again, the work of Guo et al. should be mentioned, since this work reported some metabolites to be associated with the presence of abnormalities in capillaroscopy. Capillaroscopy is a non-invasive and easy-to-perform examination

with high diagnostic value in the assessment of secondary Raynaud's phenomenon and the diagnostic differentiation of SSc. Furthermore, there is evidence that specific nailfold videocapillaroscopy patterns have an association with SSc-ILD and SSc-PAH independent of the SSc-autoantibodies [93], so that the question arises whether the presence of a simultaneous metabolic fingerprint can be delineated. Guo et al. [41] identified LysoPC(16:1(9Z)/0:0), Thromboxane A2, and 4-Vinylphenol sulfate upregulated in the presence of an abnormal capillaroscopy. However, only a dichotomous distinction was made between normal and abnormal nailfold capillaries. A detailed description of the capillaroscopic pattern, for example, early versus late or active pattern, was not provided. Nevertheless, a connection to (micro)vasculopathy seems conceivable due to the identified metabolites, since in the case of thromboxane, the contraction of smooth muscles in blood vessels and airways is mediated via the thromboxane receptors. The precise pathophysiological functions represented by the other two metabolites in different states remain to be specified. Finally, it should be mentioned that Caramaschi et al. [94] exclusively examined plasma homocysteine (Hcy) levels using a high-performance liquid chromatography method with fluorescent detection [94] and found a significant correlation between plasma Hcy concentration and the nailfold videocapillaroscopic pattern in SSc, with a progressive increase from the early to the active and, above all, the late pattern. This study is not included in our review because it focused exclusively on homocysteine. Also, not included in our review is the study by Volpe et al. [95] since this study investigated the urine metabolome.

Taken together, due to the aforementioned inherent limitations of metabolomic studies in general and the design of the studies conducted so far, no reliable statement can be made regarding the diagnostic utility of metabolomic profiling with regard to early diagnosis of SSc. If used for (early) diagnosis, more elaborate study designs would have been necessary in order to show that metabolic signatures are not associated with other—and in terms of pathophysiology similar—diseases. On the other hand, some studies demonstrated correlations between specific metabolites and disease activity, thus providing the groundwork for a potential prognostic utility of metabolomic profiling with regard to visceral organ manifestations. Therefore, further studies with prospective study designs remain mandatory to better evaluate individual metabolomic parameters not only with regard to their prognostic utility but also in terms of treatment response.

5. Conclusions

The challenge of metabolic characterization of SSc lies in its rarity and the highly variable disease course. However, this is precisely why the need for integrated studies on non-invasive, prognostic, and early diagnostic biomarkers remains urgent, with the intention to improve treatment and intervene in the progression of the disease through a personalized approach. As demonstrated, metabolic characterization in SSc offers promising perspectives with regard to diagnosis, disease endotyping, and the detection of additional biomarkers. Although the metabolome can be influenced by various factors, and the studies to date only allow speculation about a causal relationship between the observed metabolic disturbances and SSc-specific inflammation, the data at least indicate the existence of common metabolome patterns within the disease. Currently, the interpretation of these metabolic patterns or associations should be undertaken with great caution, as the results are based on the use of various analytical metabolomic techniques and the cohorts were partly small and can only be compared to a limited extent or not at all with regard to aspects such as disease duration, phenotype, and specific therapies.

However, some of the reported metabolic fingerprints not only correlate with disease activity, but also in vitro data suggest the modulation of autoimmunity, vasculopathy, fibrosis, and intestinal dysbiosis by the respective metabolic pathways. Consequently, further

studies remain mandatory to characterize the role of these alterations in the pathophysiology of the disease. Based on the studies conducted to date, mainly, but not exclusively, amino acid and lipid metabolism, as well as dysregulation of the TCA cycle, appear to have great potential to define metabolomic networks as treatment targets or as biomarkers not only for diagnosis, but also for prognosis and response to treatment.

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