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Predictors and Clinical Implications of Metabolic Syndrome in Systemic Sclerosis: Prevalence, Pathophysiological Links, and Predictive Markers

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ABSTRACT

***Background*:** Systemic sclerosis (SSc) is a chronic, multisystem autoimmune disorder characterized by vascular dysfunction, immune activation, and progressive fibrosis of the skin and internal organs. Increasing evidence has highlighted the frequent coexistence of metabolic syndrome (MetS) in patients with SSc, a combination that substantially elevates the risk for cardiovascular morbidity and mortality. The intertwining pathophysiological mechanisms of SSc and MetS, including chronic inflammation, endothelial dysfunction, and adipokine imbalance, suggest a complex bidirectional relationship that extends beyond simple coincidence. This review aims to provide an updated and comprehensive analysis of the prevalence, predictors, and clinical implications of metabolic syndrome in systemic sclerosis. Special emphasis is placed on pathophysiological links, key clinical predictors, and novel biomarkers that can facilitate early identification and risk stratification of MetS in SSc patients. An extensive literature search was conducted in PubMed, Scopus, and Web of Science databases to identify observational studies, clinical trials, and meta-analyses published in the last 20 years. The review synthesizes current knowledge regarding the epidemiology of MetS in SSc, underlying molecular and cellular mechanisms, and predictive markers with potential clinical utility. Furthermore, it addresses the impact of MetS on the prognosis of SSc and discusses therapeutic and preventive strategies tailored to this high-risk population.

Conclusion: Metabolic syndrome is prevalent in systemic sclerosis and is associated with adverse clinical outcomes, including increased cardiovascular risk, organ involvement, and poorer quality of life. Recognition of the predictors and early detection through emerging biomarkers are crucial steps in risk reduction and management. Future research should focus on longitudinal studies to validate predictive models, clarify causal relationships, and explore personalized interventions aimed at mitigating the dual burden of metabolic and autoimmune dysregulation in SSc. Enhanced understanding of the metabolic-cardiovascular axis in systemic sclerosis promises to improve patient stratification, targeted therapy, and long-term outcomes.

Keywords: Metabolic Syndrome, Predictors, Clinical Implications, Systemic Sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a complex, heterogeneous connective tissue disease marked by immune dysregulation, widespread vascular injury, and progressive fibrosis affecting the skin and multiple internal organs. The clinical manifestations of SSc are highly variable, ranging from limited cutaneous involvement to diffuse disease with significant internal organ compromise. Over recent decades, there has been a growing recognition of the importance of comorbidities in influencing disease course, prognosis, and quality of life among patients with SSc. Among these comorbidities, metabolic syndrome (MetS)—a constellation of central obesity, insulin resistance, dyslipidemia, and hypertension—has emerged as a significant clinical concern in this population[1,2].

The prevalence of MetS in patients with SSc is notably higher than in the general population, with recent studies reporting rates ranging from 20% to 45%, depending on the population studied and diagnostic criteria used[3,4]. The coexistence of MetS in SSc is not merely an additive risk; rather, the metabolic and autoimmune processes appear to interact synergistically, exacerbating vascular injury, promoting inflammation, and increasing the risk of cardiovascular events, which are now recognized as a leading cause of morbidity and mortality in SSc[5,6]. Moreover, metabolic syndrome may accelerate disease progression, contribute to the severity of organ involvement, and complicate disease management, underscoring its clinical relevance[7].

Despite accumulating evidence of the clinical significance of MetS in SSc, several key gaps remain in our understanding. The precise prevalence and predictors of MetS in different SSc subtypes, the mechanistic pathways linking these conditions, and the most reliable biomarkers for early identification and prognosis remain incompletely elucidated. Furthermore, there is an urgent need to identify strategies for the effective prevention and management of MetS in SSc, tailored to the unique immunopathological context of this disease[8].

The aim of this review is to provide a comprehensive and updated synthesis of current knowledge on the prevalence, pathophysiological links, clinical predictors, and biomarkers of metabolic syndrome in systemic sclerosis. By highlighting both established and emerging evidence, this article seeks to inform clinical practice, guide risk assessment, and identify priorities for future research in this rapidly evolving field. While the intersection between metabolic and autoimmune disorders has garnered increasing attention, there remains a paucity of longitudinal studies and validated predictive models specific to SSc. Further exploration of this interface is essential for improving outcomes and developing personalized management approaches for this high-risk group[9,10].

Prevalence of Metabolic Syndrome in Systemic Sclerosis

Metabolic syndrome (MetS) is increasingly recognized as a prevalent comorbidity in systemic sclerosis (SSc), with significant implications for both morbidity and mortality. Multiple studies across diverse geographic regions and SSc subpopulations have reported an increased frequency of MetS among SSc patients compared to healthy controls. The reported prevalence varies widely, ranging from 20% to 45%, influenced by the diagnostic criteria employed (such as the NCEP ATP III, IDF, or WHO definitions) and differences in study populations[11,12].

A multicenter study involving over 500 SSc patients from European cohorts demonstrated a MetS prevalence of approximately 32%, significantly higher than age- and sex-matched controls[13]. This elevated prevalence has been corroborated by studies in North America and Asia, confirming that MetS is not limited to any particular ethnicity or SSc subset[14]. Notably, the risk appears to be higher in diffuse cutaneous SSc compared to limited cutaneous SSc, likely reflecting the greater burden of systemic inflammation and more extensive organ involvement seen in the diffuse subtype[15].

In addition to subtype, disease duration and patient age are significant factors influencing MetS prevalence. Longer disease duration has been linked with a higher likelihood of developing MetS, possibly due to cumulative exposure to inflammation and microvascular damage[16]. Similarly, older age at diagnosis is associated with a greater risk of metabolic derangements, which may compound the cardiovascular risk profile in these patients[17]. Interestingly, some studies have suggested that the use of corticosteroids and other immunosuppressive agents, commonly prescribed in SSc management, may contribute to the development of MetS through effects on glucose and lipid metabolism[18].

Comparison of MetS components in SSc populations reveals a distinct pattern: central obesity, hypertension, and dyslipidemia are the most frequently encountered features, whereas hyperglycemia is relatively less common but still clinically relevant[19]. The prevalence of individual MetS components may also differ between male and female patients, with females showing a greater predisposition to central obesity and dyslipidemia[20]. These epidemiological nuances highlight the need for personalized

screening and risk stratification in SSc care.

Furthermore, the presence of MetS in SSc has been shown to correlate with increased frequency of subclinical atherosclerosis and impaired endothelial function, as assessed by carotid intima-media thickness and flow-mediated dilation[21]. This reinforces the clinical imperative to identify and manage MetS early in the disease course to mitigate downstream vascular complications. Despite these advances, there is a paucity of large, prospective studies systematically evaluating the incidence and longitudinal course of MetS in SSc, underscoring an important research gap[22].

Taken together, the available evidence strongly supports the notion that MetS is a frequent and clinically significant comorbidity in systemic sclerosis, with prevalence rates consistently exceeding those observed in the general population. Routine assessment for MetS and its components should be considered standard of care in SSc management to improve patient outcomes and reduce cardiovascular risk[23].

Pathophysiological Links Between Metabolic Syndrome and Systemic Sclerosis

The relationship between metabolic syndrome (MetS) and systemic sclerosis (SSc) extends beyond epidemiological association, with growing evidence suggesting shared and interacting pathophysiological pathways. Chronic inflammation is a central feature in both conditions, driving endothelial dysfunction, vascular remodeling, and tissue fibrosis[24]. In SSc, persistent immune activation leads to the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β), all of which have been implicated in insulin resistance, adipose tissue dysfunction, and the development of MetS[25,26].

Endothelial dysfunction represents a common denominator in the pathogenesis of both SSc and MetS. In SSc, early and progressive injury to the microvasculature results in reduced nitric oxide (NO) bioavailability, increased oxidative stress, and impaired vasodilation, all of which are also central to the development of hypertension and atherosclerosis seen in MetS[27]. Furthermore, increased circulating levels of endothelin-1, a potent vasoconstrictor, contribute to both vascular complications and metabolic disturbances in SSc[28]. The resultant vascular damage not only drives SSc pathology but also accelerates the metabolic derangements characteristic of MetS[29].

Adipose tissue dysfunction is increasingly recognized as a key mediator at the intersection of SSc and MetS. Altered adipokine profiles—including elevated leptin and decreased adiponectin—have been observed in SSc patients and are associated with increased inflammation, insulin resistance, and atherogenesis[30]. Adiponectin, in particular, possesses anti-inflammatory and vasculoprotective properties, and its reduction in SSc may exacerbate both fibrotic and metabolic processes[31]. Additionally, leptin promotes fibroblast activation and collagen synthesis, providing a direct mechanistic link between metabolic disturbances and SSc-related fibrosis[32].

Oxidative stress further amplifies the interplay between MetS and SSc. Enhanced production of reactive oxygen species (ROS) is a hallmark of both diseases, leading to cellular injury, lipid peroxidation, and further endothelial dysfunction[33]. In SSc, ROS-driven DNA and protein damage can perpetuate autoimmunity, while in MetS, oxidative stress accelerates insulin resistance and promotes vascular complications[34].

The renin-angiotensin system (RAS) also plays a significant role in the shared pathogenesis. Angiotensin II contributes to vasoconstriction, inflammation, and fibrosis, and increased RAS activation has been documented in both SSc and MetS[35]. Targeting RAS pharmacologically has been shown to have potential benefits in mitigating both fibrotic and metabolic consequences[36].

Mitochondrial dysfunction, emerging as a novel contributor, affects cellular energy metabolism and redox balance in both conditions. Impaired mitochondrial biogenesis and function have been described in SSc fibroblasts and endothelial cells, leading to defective tissue repair and increased susceptibility to metabolic disturbances[37]. This mitochondrial impairment may also underlie the increased prevalence of fatigue and muscle weakness in SSc patients with coexistent MetS[38].

Autoimmunity itself may influence metabolic risk, as autoantibodies commonly found in SSc, such as anti-centromere and anti-topoisomerase I, have been associated with specific metabolic phenotypes and variable risk of cardiovascular complications[39]. The dynamic interplay between immune dysregulation, metabolic derangement, and fibrotic processes establishes a complex bidirectional relationship that is not yet fully understood.

Taken together, the convergence of chronic inflammation, endothelial dysfunction, adipokine imbalance, oxidative stress, mitochondrial dysfunction, and RAS activation provides a plausible mechanistic framework explaining the high frequency and clinical importance of MetS in SSc. Understanding these links is vital for identifying novel therapeutic targets and refining risk stratification in this challenging patient population[40].

Clinical Predictors and Risk Factors of Metabolic Syndrome in Systemic Sclerosis

Identifying clinical predictors and risk factors for metabolic syndrome (MetS) in patients with systemic sclerosis (SSc) is essential for early intervention, targeted screening, and improved clinical outcomes. Several demographic, clinical, and disease-specific variables have been associated with an increased risk of developing MetS in the SSc population, highlighting the need for individualized patient assessment[41].

Age is a well-established risk factor, with older patients demonstrating a higher prevalence of MetS. This association may be attributable to the cumulative effects of aging on metabolic and vascular function, in addition to the chronicity of SSc itself[42]. Female sex, which predominates in SSc cohorts, is also associated with a slightly increased risk, possibly due to hormonal influences on adiposity, lipid metabolism, and immune function[43]. Postmenopausal status may further exacerbate this risk through changes in fat distribution and reduced estrogen-mediated vascular protection[44].

Disease duration emerges as a key clinical predictor, with longer-standing SSc being linked to a greater likelihood of MetS. Chronic inflammation and ongoing vascular damage over time may drive metabolic derangements, particularly in patients with diffuse cutaneous SSc, who tend to have more severe systemic involvement[45]. The subtype of SSc (diffuse vs. limited cutaneous) also influences risk, with diffuse disease consistently showing higher rates of MetS and more pronounced metabolic abnormalities[46].

Glucocorticoid use, while often necessary for the management of certain SSc manifestations, is a recognized iatrogenic contributor to MetS. Even low to moderate doses can exacerbate insulin resistance, promote central adiposity, and elevate blood pressure and lipid levels[47]. Other immunosuppressive medications, such as cyclosporine and tacrolimus, have also been implicated in dyslipidemia and glucose intolerance, although their use is less frequent in SSc compared to other autoimmune conditions[48].

Comorbidities such as hypothyroidism and renal dysfunction—both common in SSc—may independently increase the risk of MetS. Hypothyroidism, in particular, is associated with alterations in lipid and glucose metabolism, while chronic kidney disease contributes to hypertension and insulin resistance[49]. Additionally, physical inactivity due to musculoskeletal pain, skin tightness, or fatigue in SSc patients may further predispose to weight gain and metabolic imbalance[50].

Certain serological markers and autoantibody profiles have also been studied as potential predictors of MetS risk. For example, anti-centromere positivity has been associated with less severe metabolic disturbance, while anti-topoisomerase I (Scl-70) and anti-RNA polymerase III antibodies may be linked to more pronounced metabolic and cardiovascular risk, although these findings require further validation[51].

Importantly, family history of metabolic or cardiovascular disease, as well as traditional risk factors such as smoking and poor dietary habits, remain relevant in the SSc population and may compound the effects of disease-related and treatment-related risk factors[52]. The cumulative effect of these predictors underscores the need for a multifactorial approach to risk assessment in SSc patients.

Recent studies have also highlighted the role of body composition, particularly the presence of increased visceral adiposity (as measured by imaging modalities such as dual-energy X-ray absorptiometry or MRI), as an independent predictor of MetS in SSc[53]. This finding suggests that routine anthropometric measurements may underestimate metabolic risk in these patients, further supporting the integration of advanced imaging and biomarker-based assessment in clinical practice[54].

In summary, the clinical predictors and risk factors for MetS in systemic sclerosis are multifaceted and encompass demographic, disease-specific, treatment-related, and lifestyle variables. Early identification of high-risk patients enables timely preventive and therapeutic interventions, with the potential to significantly improve outcomes in this vulnerable population[55].

Predictive Biomarkers for Metabolic Syndrome in Systemic Sclerosis

The identification of reliable predictive biomarkers for metabolic syndrome (MetS) in systemic sclerosis (SSc) is a crucial step toward early risk stratification, precision medicine, and the implementation of targeted preventive strategies. Both traditional and novel biomarkers have been studied in SSc patients to predict the development and progression of MetS, with an increasing emphasis on integrating serological, genetic, and imaging markers for comprehensive risk assessment[56].

Traditional Biomarkers:

Among traditional markers, fasting blood glucose, insulin levels, lipid profile (including triglycerides, total cholesterol, HDL-C, and LDL-C), and markers of hepatic function are routinely assessed in SSc patients, particularly those with risk factors for MetS[57]. Insulin resistance, as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), has been shown to predict the development of MetS and is frequently elevated in SSc, especially in patients with diffuse disease or long disease duration[58]. Additionally, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are non-specific but useful for detecting the presence of systemic inflammation, which drives both SSc pathology and MetS risk[59].

Adipokines and Cytokines:

Adipokines such as adiponectin and leptin have emerged as promising biomarkers for MetS in SSc. Lower serum adiponectin levels are independently associated with MetS, visceral adiposity, and increased vascular risk, while elevated leptin correlates with both metabolic and fibrotic disease manifestations[60]. Pro-inflammatory cytokines, including IL-6, TNF-α, and TGF-β, are not only elevated in SSc but are also implicated in insulin resistance and the promotion of adipose tissue inflammation—a central feature of MetS[61]. The measurement of these cytokines may provide additional prognostic value, particularly in research settings[62].

Endothelial and Vascular Markers:

Assessment of endothelial dysfunction is integral in SSc patients. Circulating levels of endothelin-1 and asymmetric dimethylarginine (ADMA), markers of vascular injury and reduced nitric oxide availability, have been associated with both SSc disease activity and the risk of MetS[63]. Flow-mediated dilation (FMD) and carotid intima-media thickness (CIMT), as assessed by non-invasive imaging, serve as surrogate markers of early atherosclerosis and have been linked to the presence of MetS in SSc patients, underscoring the vascular component of metabolic risk[64].

Autoantibodies and Genetic Markers:

Recent studies suggest that certain SSc-specific autoantibodies may influence the likelihood of developing MetS. Anti-topoisomerase I (Scl-70) positivity has been associated with a higher risk of insulin resistance and metabolic derangements, while anti-centromere antibodies may be linked with a relatively favorable metabolic profile[65]. Additionally, genetic polymorphisms related to adipokines, cytokines, and lipid metabolism genes are under investigation as potential predictors of MetS susceptibility in SSc, though most findings remain exploratory and await replication in larger cohorts[66].

Emerging Biomarkers:

Novel biomarkers including microRNAs (miRNAs), especially those regulating inflammation and adipogenesis (e.g., miR-146a, miR-155), are being explored for their role in both SSc pathogenesis and metabolic regulation[67]. These small non-coding RNAs may serve as early indicators of metabolic dysfunction and offer mechanistic insights into disease processes. Similarly, metabolomics and proteomics-based approaches are providing new candidates, such as specific lipid metabolites or altered amino acid profiles, as potential early markers of MetS in SSc[68].

Imaging-Based Biomarkers:

Advanced imaging modalities, including MRI-based measurement of visceral adiposity and assessment of hepatic steatosis, provide non-invasive and sensitive tools for identifying SSc patients at risk for MetS, even before overt clinical features appear[69]. Such approaches allow for a more refined evaluation of metabolic risk, particularly in individuals with atypical body composition.

Clinical Utility and Future Directions:

While numerous biomarkers have shown promise, their translation into routine clinical practice requires further validation

through large, prospective studies. The integration of multiple biomarkers, combined with clinical and imaging data, is likely to enhance predictive accuracy and enable the implementation of personalized prevention strategies in SSc patients[70].

Clinical Implications and Outcomes of Metabolic Syndrome in Systemic Sclerosis

The presence of metabolic syndrome (MetS) in patients with systemic sclerosis (SSc) carries profound clinical implications, significantly influencing both disease course and overall prognosis. MetS serves as a critical driver of cardiovascular morbidity and mortality, which has emerged as a leading cause of death in SSc, surpassing the historically dominant causes such as pulmonary arterial hypertension and renal crisis[71]. The clustering of cardiovascular risk factors inherent to MetS—including hypertension, dyslipidemia, central obesity, and insulin resistance—further accelerates the atherosclerotic process in the already compromised vasculature of SSc patients[72].

Numerous studies have demonstrated that SSc patients with MetS have higher rates of overt cardiovascular events, including myocardial infarction, stroke, and peripheral arterial disease, compared to those without MetS[73]. Subclinical atherosclerosis, as assessed by carotid intima-media thickness (CIMT) and coronary artery calcification, is more prevalent and progresses more rapidly in SSc patients with MetS[74]. Furthermore, MetS is associated with increased prevalence and severity of left ventricular diastolic dysfunction and other forms of cardiac involvement in SSc, leading to heightened risk for heart failure[75].

In addition to cardiovascular consequences, the presence of MetS in SSc has been linked to worse outcomes with regard to internal organ involvement. SSc patients with MetS are at greater risk for developing interstitial lung disease, pulmonary hypertension, and scleroderma renal crisis, all of which contribute to increased disease burden and healthcare utilization[76]. The metabolic disturbances inherent in MetS, such as chronic hyperglycemia and dyslipidemia, may aggravate microvascular damage and exacerbate fibrosis, creating a vicious cycle that perpetuates both metabolic and autoimmune dysfunction[77].

Quality of life is also significantly impacted in SSc patients with MetS. Studies indicate that these individuals experience higher levels of fatigue, pain, physical disability, and depressive symptoms than their counterparts without MetS, compounding the functional limitations imposed by SSc itself[78]. Inflammatory mediators common to both conditions—such as IL-6 and TNF-α—may contribute to mood disturbances, fatigue, and cognitive dysfunction, further decreasing quality of life[79].

From a therapeutic perspective, the coexistence of MetS complicates disease management in SSc. Pharmacologic agents commonly used to control SSc manifestations—such as glucocorticoids and certain immunosuppressants—may worsen metabolic parameters, necessitating careful risk-benefit assessment and close monitoring[80]. The presence of MetS may also limit the use of some disease-modifying agents due to their potential for adverse metabolic or cardiovascular effects[81].

Importantly, the identification of MetS in SSc patients offers an opportunity for early, aggressive cardiovascular risk modification. Guidelines increasingly recommend routine screening for MetS and its components in all patients with SSc, as well as comprehensive risk assessment including imaging, serologic, and functional studies[82]. Multidisciplinary management—encompassing rheumatologists, cardiologists, endocrinologists, and nutritionists—is essential for optimizing care and improving long-term outcomes[83].

Despite the growing recognition of the clinical impact of MetS in SSc, significant gaps remain in the understanding of the natural history and optimal management strategies for these high-risk patients. Most studies to date are cross-sectional or retrospective, highlighting the need for prospective, longitudinal research to clarify the impact of MetS on SSc progression and to identify best practices for risk reduction[84].

In summary, metabolic syndrome in systemic sclerosis is associated with increased cardiovascular events, greater internal organ involvement, worse quality of life, and added complexity in management. Proactive identification and aggressive intervention targeting MetS hold the promise of improved outcomes for this vulnerable patient population[85].

Therapeutic and Preventive Strategies

Management of metabolic syndrome (MetS) in systemic sclerosis (SSc) requires an integrated and multidisciplinary approach that addresses both metabolic and autoimmune components of the disease. The goals are to reduce cardiovascular risk, limit organ damage, and improve overall quality of life. Given the unique pathophysiological features of SSc, standard MetS management must be tailored to account for the interplay between chronic inflammation, vascular dysfunction, and fibrotic processes[86].

Lifestyle Modification:

Lifestyle interventions are the cornerstone of MetS management and are particularly relevant in SSc patients, who often have additional barriers to physical activity due to musculoskeletal and skin involvement. Dietary modifications focusing on caloric restriction, reduced intake of saturated fats, and increased consumption of fruits, vegetables, and whole grains are universally recommended[87]. Physical activity, when feasible, should be encouraged to improve insulin sensitivity, promote cardiovascular health, and preserve muscle mass. Exercise regimens may need to be adapted in collaboration with physical therapists or rehabilitation specialists to accommodate joint contractures, skin tightness, and fatigue commonly seen in SSc[88]. Smoking cessation and moderation of alcohol intake are essential lifestyle targets that further decrease cardiovascular risk[89].

Pharmacological Management:

Medical treatment of MetS components in SSc generally follows standard recommendations for hypertension, dyslipidemia, and diabetes but requires particular caution regarding drug interactions, organ involvement, and potential side effects. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are preferred agents for blood pressure control in SSc, given their additional benefits on endothelial function and renal protection[90]. Statins are effective for dyslipidemia and may offer ancillary anti-inflammatory and antifibrotic effects, though their tolerability should be closely monitored in SSc patients with myopathy or hepatic involvement[91].

Metformin, a first-line agent for type 2 diabetes, is generally safe and may confer additional benefits in reducing fibrosis and improving endothelial function, but its use should be avoided or monitored in those with significant gastrointestinal dysmotility or renal impairment[92]. Thiazolidinediones and certain other antidiabetic medications are used with caution, as they may exacerbate edema or contribute to cardiac dysfunction in SSc[93]. Novel agents, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, have shown cardiovascular benefit in the general population, but robust data in SSc are lacking[94].

Targeted Therapies and Disease-Modifying Agents:

Given the overlap in pathogenesis between SSc and MetS, targeting shared mechanisms such as inflammation, oxidative stress, and adipokine imbalance represents a promising therapeutic strategy. Agents that modulate the renin-angiotensin system, including ACE inhibitors and ARBs, have shown benefits in both metabolic and fibrotic outcomes[95]. Anti-fibrotic drugs (such as nintedanib) and immunomodulators (including mycophenolate mofetil and rituximab) are used primarily for SSc but may have indirect benefits on metabolic parameters by reducing overall disease activity[96].

Adipokine-targeted therapies, antioxidant agents, and inhibitors of cytokine signaling (such as IL-6 or TNF-α inhibitors) are being studied for their potential dual impact on fibrosis and metabolic dysfunction, although evidence remains preliminary[97]. The safety and efficacy of such approaches need to be established in the context of the unique risks posed by SSc.

Preventive Strategies and Screening:

Routine and proactive screening for MetS components is strongly recommended in all SSc patients, with assessment of blood pressure, fasting glucose, lipid profile, and waist circumference at regular intervals[98]. Early detection of subclinical atherosclerosis using carotid ultrasound or other non-invasive imaging can identify high-risk patients and prompt earlier intervention[99]. Multidisciplinary care—engaging rheumatologists, cardiologists, endocrinologists, nephrologists, nutritionists, and rehabilitation specialists—is essential for holistic risk assessment and individualized management plans[100].

Patient Education and Empowerment:

Education about the risks of MetS, the importance of lifestyle changes, and the potential side effects of medications is crucial for improving adherence and long-term outcomes. Support groups, counseling, and structured rehabilitation programs can help overcome barriers to physical activity and dietary modification, addressing both psychological and physical challenges faced by SSc patients[101].

Future Directions:

Research into new pharmacologic agents that target shared pathways in SSc and MetS, including those aimed at modulating adipokines, mitochondrial function, and the gut microbiome, is ongoing[102]. Personalized medicine approaches, incorporating

predictive biomarkers and genetic profiling, hold promise for more effective prevention and management of MetS in SSc. Ultimately, large-scale, prospective studies are needed to validate these strategies and optimize care for this high-risk population[103].

Future Perspectives

Despite substantial advances in understanding the interplay between metabolic syndrome (MetS) and systemic sclerosis (SSc), several important questions remain, and future research directions are crucial for improving clinical care and patient outcomes. One priority is the conduct of large-scale, longitudinal cohort studies to clarify the natural history and temporal relationship of MetS development in SSc, identify causative links, and establish reliable risk prediction models tailored to SSc subpopulations[104].

There is a need for rigorous validation of emerging biomarkers—serological, genetic, and imaging-based—to enhance early detection, risk stratification, and prognosis of MetS in SSc. Prospective multicenter studies and international collaborations can facilitate the standardization of biomarker assessment and the integration of multi-omics approaches, such as genomics, proteomics, and metabolomics, into clinical practice[105]. The identification of composite biomarker panels that combine metabolic, vascular, and immunological indicators may offer superior predictive power compared to single-marker approaches[106].

A promising area of investigation is the role of the gut microbiome in mediating the links between autoimmunity, metabolism, and vascular dysfunction in SSc. Dysbiosis has been implicated in both SSc pathogenesis and MetS, and interventions targeting the microbiome—such as probiotics, prebiotics, or fecal microbiota transplantation—may represent novel therapeutic avenues[107]. In parallel, further research is warranted into the mechanisms of mitochondrial dysfunction, oxidative stress, and adipokine signaling as therapeutic targets common to both conditions[108].

The development and clinical testing of new pharmacological agents, particularly those targeting inflammatory pathways (e.g., anti-IL-6, anti-TNF-α, and anti-TGF-β therapies), antifibrotic agents, and drugs modulating insulin sensitivity or lipid metabolism, hold significant promise. Personalized medicine approaches, utilizing genetic and biomarker profiling, may enable tailored preventive and therapeutic strategies, minimizing adverse effects and maximizing efficacy[109].

From a clinical management perspective, randomized controlled trials (RCTs) are needed to establish optimal treatment protocols for MetS in SSc, including the role of statins, ACE inhibitors, SGLT2 inhibitors, and lifestyle interventions. Given the complexity of SSc, future trials should incorporate patient-reported outcomes, quality of life measures, and long-term safety data[110]. The impact of early and aggressive intervention in high-risk patients on SSc progression, organ damage, and mortality remains an area of particular interest.

Educational and psychosocial interventions targeting patient empowerment, adherence, and self-management should be systematically studied. Digital health technologies, including telemedicine, wearable devices, and mobile applications, could facilitate regular monitoring of metabolic parameters and enhance patient engagement, especially for those with limited mobility due to SSc[111].

Finally, global efforts to harmonize diagnostic criteria for MetS in SSc are needed to ensure consistency in research and clinical practice. The integration of cardiovascular risk assessment into routine SSc care, multidisciplinary team approaches, and the dissemination of evidence-based guidelines will be essential in translating research advances into improved patient outcomes[112].

In conclusion, future research should focus on bridging the knowledge gaps related to pathogenesis, early detection, and management of MetS in SSc, with a view toward personalized, holistic, and evidence-based care. Collaborative efforts across disciplines and international borders will be instrumental in addressing these challenges and improving the lives of patients with SSc.

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