Endothelial Injury Biomarkers in Pediatric Lupus: Focus on Endocan as an Early Predictor of Vascular Dysfunction

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Abstract

Background: Pediatric-onset systemic lupus erythematosus (pSLE) is a chronic multisystem autoimmune disease characterized by heightened disease severity, cumulative organ damage, and increased long-term cardiovascular morbidity compared with adult-onset disease. Endothelial dysfunction represents a critical early event in the pathogenesis of premature atherosclerosis observed in children with lupus, often preceding overt clinical cardiovascular disease. Traditional cardiovascular risk assessment tools are insufficient in pediatric lupus, underscoring the need for sensitive and disease-specific biomarkers that can identify early vascular injury. Endocan, also known as endothelial cell–specific molecule-1, is a soluble dermatan sulfate proteoglycan secreted by activated endothelial cells and has emerged as a promising biomarker of endothelial activation, inflammation, and vascular dysfunction in inflammatory and autoimmune diseases.

Aim: This review aims to synthesize current evidence on endothelial injury biomarkers in pediatric lupus, with a focused emphasis on endocan as an early predictor of vascular dysfunction. We explore the biological role of endocan in endothelial homeostasis, its regulation by inflammatory and immune-mediated pathways relevant to lupus, and its potential clinical utility in identifying subclinical vascular injury in children with SLE. Additionally, this review highlights how endocan compares with conventional and emerging endothelial biomarkers and examines its relevance within the unique immunopathological and developmental context of pediatric disease.

Conclusion: Accumulating evidence suggests that endocan is closely linked to endothelial activation, immune dysregulation, and vascular inflammation—key mechanisms underlying cardiovascular risk in pediatric lupus. Elevated endocan levels have been associated with disease activity, inflammatory burden, and markers of vascular dysfunction in lupus and related autoimmune conditions, supporting its role as an early and sensitive indicator of endothelial injury. Incorporating endocan into multimarker strategies may improve early cardiovascular risk stratification in pediatric SLE, enabling timely preventive and therapeutic interventions. However, pediatric-specific longitudinal studies are limited, and standardized reference ranges are lacking. Future research should focus on validating endocan in large pediatric cohorts, clarifying its prognostic value, and integrating it into clinical risk assessment models to mitigate long-term cardiovascular complications in children with lupus.

Keywords: *Vascular Dysfunction, Endothelial Injury , Pediatric Lupus*

Introduction

Pediatric-onset systemic lupus erythematosus (pSLE) is a chronic, multisystem autoimmune disease representing approximately 15–20% of all lupus cases and is typically associated with greater disease severity compared with adult-onset SLE. Children with lupus often present with high disease activity at diagnosis and experience early involvement of major organs such as the kidneys, central nervous system, and hematologic system. Advances in immunosuppressive therapy have significantly improved survival; however, long-term morbidity remains substantial. Cardiovascular disease has emerged as a major contributor to late mortality in pSLE, emphasizing the importance of identifying early pathogenic mechanisms that drive vascular injury in this vulnerable population [1].

Endothelial dysfunction is now recognized as a central and early event in the development of accelerated atherosclerosis in lupus. In pediatric patients, endothelial injury begins early in the disease course and may remain clinically silent for years before overt cardiovascular manifestations become evident. Chronic immune activation, persistent systemic inflammation, circulating immune complexes, and complement-mediated damage collectively disrupt endothelial integrity and function. These processes promote a proatherogenic vascular environment characterized by impaired vasodilation, increased leukocyte adhesion, and heightened oxidative stress, all of which contribute to premature vascular aging in children with lupus [2].

Traditional cardiovascular risk factors such as hypertension, dyslipidemia, insulin resistance, and obesity are frequently observed in pediatric lupus; however, they do not fully explain the magnitude of cardiovascular risk seen in this population. Studies have demonstrated that even children with well-controlled traditional risk factors exhibit evidence of subclinical vascular disease, suggesting that lupus-specific immune and inflammatory mechanisms play a dominant role. As a result, conventional cardiovascular risk assessment tools used in the general pediatric population are insufficient for accurately identifying early vascular injury in children with SLE [3].

Noninvasive imaging modalities, including carotid intima–media thickness measurement and flow-mediated dilation, have provided important insights into subclinical atherosclerosis and endothelial dysfunction in pediatric lupus. These studies consistently demonstrate increased arterial thickness and impaired endothelial-dependent vasodilation compared with healthy controls. However, such techniques are not routinely available in clinical practice, may require specialized expertise, and are limited in their ability to detect early molecular changes within the endothelium. This has prompted increasing interest in circulating biomarkers as practical tools for early vascular risk stratification in pSLE [4].

Among emerging biomarkers of endothelial injury, endocan—also known as endothelial cell–specific molecule-1—has gained attention due to its direct secretion by activated endothelial cells in response to inflammatory cytokines. Endocan reflects endothelial activation, vascular inflammation, and immune–endothelial interactions, all of which are central to lupus pathogenesis. Elevated endocan levels have been reported in adult SLE and other inflammatory diseases and have been associated with disease activity and vascular dysfunction. Despite its strong biological relevance, data on endocan in pediatric lupus remain limited, representing a significant knowledge gap and a promising area for future research focused on early cardiovascular risk detection [5].

Endothelial Dysfunction in Pediatric Systemic Lupus Erythematosus

Endothelial dysfunction is a fundamental pathological process underlying the increased cardiovascular risk observed in pediatric-onset systemic lupus erythematosus. The endothelium plays a critical role in maintaining vascular homeostasis through regulation of vascular tone, coagulation, inflammation, and leukocyte trafficking. In children with lupus, persistent immune activation and systemic inflammation disrupt these regulatory functions early in the disease course. This dysfunction manifests as reduced nitric oxide bioavailability, increased oxidative stress, and a shift toward a proinflammatory and prothrombotic endothelial phenotype, even in the absence of clinical cardiovascular disease [6].

Immune complex deposition and complement activation are central drivers of endothelial injury in

pediatric lupus. Circulating immune complexes bind to endothelial cells, triggering complement-mediated cytotoxicity and promoting endothelial apoptosis. Complement split products such as C3a and C5a further amplify vascular inflammation by recruiting leukocytes and inducing cytokine release. Pediatric patients, who often exhibit higher disease activity and complement consumption than adults, may therefore experience more intense and sustained endothelial injury, contributing to early vascular dysfunction and accelerated atherosclerosis [7].

Proinflammatory cytokines play a pivotal role in perpetuating endothelial dysfunction in pSLE. Elevated levels of tumor necrosis factor-α, interleukin-6, interferon-α, and interleukin-1β have been consistently demonstrated in pediatric lupus and are known to directly impair endothelial cell function. These cytokines reduce endothelial nitric oxide synthase activity, enhance expression of adhesion molecules, and promote leukocyte adhesion and transmigration. The chronic exposure of the pediatric vasculature to this inflammatory milieu contributes to endothelial activation and sets the stage for long-term vascular damage [8].

Oxidative stress represents another key mechanism linking lupus-related inflammation to endothelial dysfunction in children. Increased production of reactive oxygen species, coupled with impaired antioxidant defenses, leads to lipid peroxidation and endothelial cell damage. In pediatric lupus, oxidative stress has been associated with disease activity and subclinical vascular abnormalities, including impaired flow-mediated dilation. These findings suggest that oxidative injury occurs early in life and may contribute to irreversible vascular remodeling if left unrecognized and untreated [9].

Clinical and subclinical studies have demonstrated measurable endothelial dysfunction in children with lupus using noninvasive vascular assessments. Reduced flow-mediated dilation and increased arterial stiffness have been reported in pediatric patients compared with healthy controls, even in those with relatively short disease duration. Importantly, these vascular changes often occur independently of traditional cardiovascular risk factors, reinforcing the concept that lupus-specific immune mechanisms are primary drivers of endothelial injury in this population [10].

Biomarkers of Endothelial Injury in Pediatric Lupus

The identification of reliable biomarkers of endothelial injury has become a priority in pediatric systemic lupus erythematosus due to the silent and progressive nature of vascular damage in this population. An ideal biomarker should reflect early endothelial activation, correlate with disease-related vascular pathology, and be measurable using minimally invasive methods. In pediatric lupus, biomarkers are particularly valuable because clinical cardiovascular events are rare during childhood, yet pathological processes leading to premature atherosclerosis are already active. Circulating biomarkers therefore offer a practical approach to identifying subclinical vascular injury and stratifying long-term cardiovascular risk [11].

Traditional biomarkers of endothelial activation, such as von Willebrand factor, have been extensively studied in systemic lupus erythematosus and are known to reflect endothelial perturbation and prothrombotic states. Elevated von Willebrand factor levels have been reported in pediatric lupus and are associated with disease activity and vascular inflammation. However, this marker lacks specificity, as it can be influenced by systemic inflammation, infection, and stress, limiting its utility as a standalone indicator of lupus-related endothelial dysfunction in children [12].

Soluble adhesion molecules, including soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1, are commonly used biomarkers of endothelial activation in autoimmune diseases. These molecules mediate leukocyte adhesion and transmigration across the endothelium and are upregulated in response to inflammatory cytokines. In pediatric lupus, elevated levels of soluble adhesion molecules have been associated with disease activity and immune activation, suggesting ongoing endothelial inflammation. Nevertheless, their widespread expression across multiple inflammatory conditions reduces their specificity for vascular injury directly related to lupus [13].

Markers of endothelial-derived coagulation and fibrinolysis pathways, such as thrombomodulin and plasminogen activator inhibitor-1, have also been explored in lupus populations. These biomarkers reflect endothelial damage and a shift toward a prothrombotic phenotype, which is particularly relevant given the

increased thrombotic risk in lupus. In children with SLE, altered levels of these markers have been observed, especially in those with antiphospholipid antibodies. However, variability related to age, pubertal status, and concurrent therapies complicates their interpretation in pediatric cohorts [14].

More recently, attention has shifted toward novel biomarkers that more directly reflect endothelial cell activation and dysfunction. These include angiopoietins, asymmetric dimethylarginine, and endothelial progenitor cell–related markers, which provide insight into endothelial repair capacity and nitric oxide metabolism. While these markers offer promising mechanistic information, their clinical application in pediatric lupus remains limited due to inconsistent findings and lack of standardized reference ranges. This has prompted growing interest in endocan as a biomarker that integrates endothelial activation, inflammation, and immune-mediated vascular injury within a single measurable molecule [15].

Biology and Regulation of Endocan

Endocan, also termed endothelial cell–specific molecule-1 (ESM-1), is a soluble endothelial-derived proteoglycan initially identified as an endothelium-associated molecule with preferential expression in the lung microvasculature and upregulation under inflammatory stimulation. Structurally, endocan is secreted into the circulation rather than retained in the endothelial glycocalyx, which makes it attractive as a measurable plasma/serum biomarker reflecting endothelial activation. Its biology is particularly relevant to pediatric lupus because pSLE is characterized by sustained cytokine exposure and immune-mediated endothelial stress, conditions that are known to modulate endocan expression and release. [16]

At the molecular level, endocan is a ~50 kDa dermatan sulfate proteoglycan composed of a core protein with a single glycosaminoglycan chain, a feature that influences ligand binding and downstream vascular effects. This dermatan sulfate chain is not merely structural; it contributes to endocan's functional interactions with growth factors and inflammatory mediators, supporting the concept that circulating endocan can behave as an active participant in endothelial signaling rather than a passive byproduct of injury. These structural–functional properties are central when interpreting endocan elevations in inflammatory diseases, including lupus, where angiogenic and inflammatory pathways are simultaneously engaged. [17]

Endocan also functions at the interface between endothelial cells and leukocytes, linking vascular biology to immune cell trafficking—an especially important axis in SLE. Experimental work supports that endocan can bind leukocyte integrins (notably LFA-1/CD11a-CD18) and modulate adhesion-related interactions, which may influence leukocyte recruitment and diapedesis across activated endothelium. In lupus, where endothelial activation and aberrant leukocyte–endothelium interactions are key drivers of vascular inflammation, this mechanistic role strengthens the plausibility of endocan as a biomarker that reflects immune-mediated endothelial injury. [18]

The expression of endocan is regulated by inflammatory cytokines and proangiogenic cues that are highly relevant to pSLE pathobiology. Evidence across experimental and clinical literature indicates that proinflammatory mediators (e.g., TNF-α and IL-1β) and angiogenic signaling (particularly VEGF-related pathways) can upregulate endocan expression in endothelial cells, consistent with its behavior as a marker of endothelial activation in inflammatory states. This regulatory profile aligns with pediatric lupus biology, where interferon-driven inflammation, cytokine networks, and vascular stress can coexist—even in clinically "stable" phases—potentially producing persistent low-grade endocan elevation. [19]

A further layer of complexity is that endocan biology includes proteolytic processing, generating fragments that may have distinct biological effects and may influence how circulating concentrations relate to vascular phenotype. Work examining cleaved endocan has highlighted that endocan-related peptides can interact with leukocyte adhesion pathways, implying that not only total endocan concentration but also its molecular forms could matter when linking biomarker levels to endothelial dysfunction. This is an important emerging concept for pediatric lupus research, where biomarker interpretation must account for developmental physiology and inflammation-driven protease activity. [20]

Endocan in Autoimmune and Inflammatory Diseases: Relevance to Lupus Pathophysiology

Endocan has been increasingly investigated across a spectrum of autoimmune and chronic inflammatory diseases, where endothelial activation and immune-mediated vascular injury are central pathogenic features. Elevated circulating endocan levels have been reported in conditions such as rheumatoid arthritis, inflammatory bowel disease, and systemic vasculitides, supporting its role as a marker of inflammation-driven endothelial dysfunction. These diseases share key mechanisms with systemic lupus erythematosus, including cytokine excess, immune cell–endothelial interactions, and chronic vascular stress, making findings from these conditions biologically relevant to pediatric lupus research [21].

In autoimmune diseases, endocan appears to reflect the intensity of systemic inflammation and endothelial activation rather than traditional cardiovascular risk factors. Studies in inflammatory rheumatic diseases have demonstrated correlations between endocan levels and inflammatory markers, disease activity indices, and vascular involvement. This inflammatory responsiveness distinguishes endocan from classical endothelial markers that may be influenced by age, metabolic status, or mechanical vascular stress. In the pediatric lupus context, where inflammation is often the dominant driver of vascular injury, this characteristic enhances the potential utility of endocan as a disease-relevant biomarker [22].

Systemic lupus erythematosus provides a particularly compelling biological framework for endocan dysregulation due to the convergence of immune dysregulation, interferon signaling, and vascular inflammation. Adult SLE studies have consistently demonstrated elevated endocan concentrations compared with healthy controls, with associations reported between endocan levels and disease activity, inflammatory burden, and markers of endothelial dysfunction. These findings suggest that endocan reflects lupus-specific endothelial injury rather than nonspecific inflammation, reinforcing its relevance as a candidate biomarker in pediatric disease, where vascular injury begins early but remains clinically silent [23].

Interferon-driven immune activation, a hallmark of lupus pathogenesis, may represent a critical upstream regulator of endocan expression. Type I interferons promote endothelial activation, impair endothelial repair mechanisms, and amplify inflammatory signaling within the vasculature. Although direct interferon–endocan regulatory pathways are still being elucidated, the coexistence of interferon signatures and elevated endocan levels in inflammatory diseases supports a mechanistic link. This is particularly relevant in pediatric lupus, where interferon signatures are often pronounced and sustained, potentially contributing to persistent endothelial stress detectable through endocan measurement [24].

Beyond inflammation, endocan has been associated with vascular complications and endothelial dysfunction in autoimmune populations, including correlations with arterial stiffness, impaired endothelial-dependent vasodilation, and microvascular abnormalities. These associations highlight endocan's potential to serve not only as a marker of inflammation but also as an indicator of functional vascular impairment. Translating these observations to pediatric lupus suggests that endocan may help bridge the gap between molecular endothelial activation and early, measurable vascular dysfunction, supporting its investigation as an early predictor of long-term cardiovascular risk in children with SLE [25].

Evidence of Endocan in Systemic Lupus Erythematosus

Clinical evidence supporting endocan as a vascular biomarker in SLE has grown over the past decade, primarily in adult cohorts, where endocan is consistently higher than in healthy controls and is interpreted as a signal of inflammation-linked endothelial activation. In these studies, endocan is framed as an "endothelium-released" marker that may capture vascular injury that is not fully explained by traditional metabolic risk factors, aligning with the concept of lupus-specific vasculopathy. This adult evidence is important for pediatrics because pSLE patients accumulate inflammatory burden earlier in life and may therefore experience a longer exposure window during which endothelial dysfunction can develop silently.

[26]

A frequently cited clinical signal for vascular relevance is the association between circulating endocan and subclinical atherosclerosis measures in SLE. In a study evaluating SLE patients with carotid ultrasound, serum endocan levels were higher in SLE than controls and showed a positive correlation with carotid intima–media thickness, supporting the idea that endocan may reflect early atherosclerotic vascular remodeling rather than only systemic inflammation. For pediatric lupus, this type of association is clinically meaningful because carotid imaging and functional vascular testing are not always accessible, and blood biomarkers could offer a more feasible screening approach for early vascular risk. [27]

Other adult SLE studies suggest that endocan tracks with inflammatory and endothelial stress pathways that are biologically plausible in lupus, including relationships with pro-inflammatory cytokine signaling and angiogenic activation. For example, observational work has reported higher endocan in SLE and described correlations between endocan and inflammatory mediators, supporting a model in which endocan integrates vascular inflammation with immune activation. This mechanism-based linkage is particularly relevant in pSLE, where interferon-related inflammation and complement-mediated injury are often prominent, but direct pediatric validation of endocan remains limited. [28]

More recent work has expanded the vascular phenotype beyond carotid thickness to include functional arterial stiffness parameters in younger SLE populations, strengthening the concept that endocan may reflect broad vascular dysfunction rather than a single surrogate endpoint. In a 2025 study of young patients with active SLE, serum endocan was analyzed alongside arterial stiffness indices and complement measures, providing contemporary evidence that endocan may align with vascular physiology and immunologic activity in a clinically actionable way. While “young” cohorts may not be strictly pediatric in all studies, they bridge the translational gap and support prioritizing dedicated pSLE studies with age-stratified analyses and longitudinal follow-up. [29]

Critically, truly pediatric endocan data in pSLE are still scarce, and this gap limits immediate clinical adoption despite strong mechanistic plausibility and supportive adult findings. Pediatric lupus differs from adult disease in immune maturation, pubertal physiology, treatment exposures, and the timing of vascular injury accumulation—factors that could alter baseline endocan levels, thresholds, and prognostic meaning. Therefore, the next logical step for the field is rigorous pediatric validation: establishing age- and puberty-adjusted reference ranges, testing relationships with pediatric vascular endpoints (flow-mediated dilation, arterial stiffness, cIMT), and evaluating whether endocan predicts progression or treatment-responsive improvement in vascular dysfunction over time. [30]

Endocan in Pediatric Populations—What We Know, and How to Interpret It in pSLE

Endocan has been measured in several pediatric inflammatory and vascular-stress conditions, and across these settings it generally behaves as a marker of endothelial activation in response to systemic inflammation. Importantly for pediatric lupus, these studies collectively show that endocan can rise in children even before overt cardiovascular disease is clinically evident, supporting its conceptual use as an “early warning” signal of endothelial injury. This pediatric evidence matters because endothelial dysfunction in pSLE is typically subclinical for years, and practical blood biomarkers are needed to complement imaging-based vascular assessments that are not universally available. While disease-specific pediatric lupus data remain limited, the broader pediatric literature provides proof-of-concept that circulating endocan is measurable, dynamic, and inflammation-responsive in children. [31]

In pediatric rheumatology, juvenile idiopathic arthritis (JIA) offers a useful comparator disease because it is chronic, inflammatory, and treated with immunomodulators—features shared with pSLE. In a pediatric JIA cohort, serum endocan levels were significantly higher than in controls, indicating that ongoing childhood inflammation can translate into measurable endothelial activation. Although JIA differs immunologically from lupus, this finding supports a pediatric principle highly relevant to pSLE: systemic inflammation alone, even without overt vascular events, can shift endothelial biomarkers in children. For lupus research, this strengthens the rationale to study endocan as a marker reflecting inflammatory vascular stress and possibly cumulative vascular risk over time. [32]

Another informative pediatric model comes from long-term survivors of childhood cancers, where

therapy-related endothelial injury and early vascular remodeling can be detected using biomarkers and carotid intima–media thickness (cIMT). In a study of childhood acute lymphoblastic leukemia survivors, serum endocan was elevated and accompanied by increased cIMT, linking endocan not only to inflammation but also to a measurable structural vascular surrogate in a pediatric context. This is relevant to pSLE because children with lupus often experience prolonged inflammatory exposure and long-term corticosteroid or immunosuppressive therapy, both of which can contribute to vascular risk. These data support the potential of endocan to serve as a pediatric-accessible marker that aligns with early subclinical vascular changes. [33]

Endocan has also been examined in pediatric renal and cardio-renal risk settings, which are particularly pertinent to pSLE given the high burden of lupus nephritis and hypertension in childhood. In pediatric populations where hypertension and vascular stress are clinically meaningful, endocan has been studied as part of endothelial dysfunction profiling, reinforcing the concept that endocan responds to vascular injury pathways relevant to renal disease. This is important for pediatric lupus because nephritis-associated endothelial injury and blood pressure abnormalities may amplify vascular dysfunction, and a biomarker that reflects endothelial activation could help identify higher-risk children earlier than imaging or event-based outcomes would. [34]

Despite these supportive pediatric signals, translating endocan into pediatric lupus practice requires careful developmental interpretation. Endothelial biology in children is influenced by growth, pubertal hormonal changes, body composition shifts, and evolving immune maturation; thus, biomarker thresholds derived from adults cannot be directly applied to pSLE. Pediatric inflammatory studies further suggest that endocan may change with acute systemic inflammatory surges, indicating that timing relative to disease flare, infection, or treatment escalation could substantially influence measured levels. Therefore, pediatric lupus studies must prioritize age- and puberty-adjusted reference frameworks, standardized sampling timing, and longitudinal designs to determine whether endocan predicts progression of vascular dysfunction rather than simply mirroring transient inflammation. [35]

Endocan in Lupus—Links to Disease Activity, Vascular Measures, and Organ Involvement (Including Nephritis)

Adult SLE studies provide the strongest clinical signal that endocan reflects lupus-associated vascular dysfunction, not just generalized inflammation. In a case–control study of women with SLE, serum endocan levels were higher than in healthy controls and were evaluated alongside carotid intima–media thickness (cIMT), supporting the concept that endocan may align with subclinical atherosclerosis in lupus—a key translational endpoint for pediatric disease where cardiovascular events are rare but vascular injury begins early. [36]

Beyond structural vascular surrogates, endocan has been studied as a molecule that integrates endothelial activation with inflammatory networks that are central to lupus pathogenesis. In an SLE cohort where endocan was measured together with pro-inflammatory cytokines and VEGF, serum endocan was higher in patients than controls, reinforcing its potential role as an endothelial dysfunction marker within the inflammatory milieu of SLE; this is particularly relevant to pediatric lupus, where interferon-driven and cytokine-mediated endothelial stress is often more intense and prolonged. [37]

More contemporary work in younger SLE populations has attempted to connect endocan to functional vascular assessments, including arterial stiffness parameters, while simultaneously contextualizing endocan within routine immunologic activity markers. In a 2025 study of young patients with clinically active SLE, investigators reported correlations between serum endocan and complement measures (including negative correlations with CH50 and C3), suggesting that endocan may reflect immune-mediated vascular injury linked to complement consumption—an important mechanistic bridge to pediatric lupus, where complement abnormalities are common during active disease. [38]

When considering organ involvement, lupus nephritis is a major driver of long-term cardiovascular risk in pSLE through combined effects of systemic inflammation, hypertension, proteinuria, endothelial activation, and cumulative steroid exposure. However, despite strong biological plausibility (renal inflammation and vascular injury are tightly connected), direct pediatric lupus nephritis studies validating

endocan as a nephritis-specific or nephritis-stratifying biomarker remain limited; therefore, current best practice is to frame endocan as a candidate vascular biomarker that should be tested alongside established nephritis biomarkers and renal vascular risk phenotypes in childhood-onset disease. [39]

Taken together, the available lupus literature supports endocan as a biologically plausible "endothelial activation readout," but it also highlights why pediatric validation is urgently needed: children differ from adults in immune maturation, baseline vascular physiology, and the timing of cumulative exposure to inflammation and therapies. A key next step is pediatric longitudinal work that measures endocan serially across flares and remission and tests whether it predicts changes in pediatric vascular endpoints (flow-mediated dilation, arterial stiffness, cIMT) beyond disease activity indices and traditional risk factors. [40]

Comparing Endocan With Other Endothelial Injury Biomarkers in Pediatric Lupus

Classical endothelial activation biomarkers in lupus most often include soluble adhesion molecules (particularly soluble VCAM-1), von Willebrand factor, E-selectin, ICAM-1, thrombomodulin, and endothelial microparticles; however, across the SLE literature their performance is heterogeneous, with variability driven by disease activity, organ involvement (especially nephritis), treatment, and assay differences. A recent systematic review of endothelial cell markers in SLE highlighted that VCAM-1 is among the most frequently reported endothelial markers and is repeatedly linked to "endothelial activation," but also emphasized broad inconsistency across markers and outcomes—supporting the need for biomarkers that better integrate vascular biology with lupus-specific inflammation and that can be standardized for pediatric use. [41]

Soluble VCAM-1 is arguably the most clinically "actionable" comparator in pediatric lupus because it is mechanistically tied to leukocyte adhesion and is repeatedly associated with renal and systemic disease activity; importantly, urinary soluble VCAM-1 (uVCAM-1) has emerged as a promising lupus nephritis biomarker, reflecting local endothelial/renal inflammatory shedding and showing utility for disease activity monitoring. For pediatric lupus, this creates a practical multimarker framework: VCAM-1 (especially uVCAM-1) may better reflect renal inflammatory activity, whereas endocan may better reflect systemic endothelial activation and broader vascular dysfunction—together capturing two major cardiovascular-risk amplifiers in pSLE (inflammation and nephritis). [42]

In contrast, endocan offers a distinct advantage over many "traditional" endothelial markers because it is secreted by activated endothelium and has shown direct associations with subclinical atherosclerosis surrogates in SLE. In the Angiology study evaluating SLE patients, higher endocan levels correlated with carotid intima–media thickness, suggesting potential alignment with early vascular remodeling rather than merely reflecting nonspecific inflammation. From a pediatric perspective, this is attractive because structural/functional vascular testing is not always available, so a blood biomarker that tracks with subclinical atherosclerosis phenotypes could improve early vascular risk identification in children with SLE. [43]

Endocan should also be interpreted relative to the broader inflammatory-endothelial axis in lupus, where its elevations may parallel cytokine-driven endothelial activation and angiogenic signaling. In a clinical SLE study assessing endocan alongside inflammatory mediators (including IL-1, TNF, and VEGF), SLE patients had higher endocan levels and the findings supported endocan as a candidate marker of endothelial dysfunction within lupus-relevant inflammatory networks. For pediatric lupus, this matters because cytokine and interferon activity can be high even early in disease, implying that endocan may capture vascular stress in a way that complements adhesion molecules and coagulation markers—particularly when used as part of a composite biomarker panel. [44]

Given the limitations of any single biomarker, the most defensible pediatric strategy is a multimarker approach that triangulates endothelial activation, vascular remodeling risk, and organ-specific contributors (notably nephritis). Emerging evidence from a 2025 study in young SLE patients suggests serum endocan may behave differently in shorter disease duration and may have limited predictive value in some "young/early" phenotypes—an important caution for pediatrics and a strong rationale for longitudinal validation in pSLE with age-/puberty-adjusted thresholds and repeated measures across flare and remission. In practice, this supports using endocan alongside complementary markers (e.g., VCAM-

1/uVCAM-1 and functional vascular measures where available) rather than as a standalone test in children. [45]

Conclusion

Endothelial dysfunction represents a critical and early pathogenic process in pediatric-onset systemic lupus erythematosus, underpinning the markedly increased long-term cardiovascular risk observed in this population. Traditional cardiovascular risk assessment tools and isolated clinical parameters are insufficient to capture the silent vascular injury that begins in childhood, highlighting the need for sensitive and disease-relevant biomarkers capable of detecting early endothelial activation before irreversible vascular damage occurs.

Endocan has emerged as a biologically plausible and clinically promising marker of endothelial injury that directly reflects endothelial activation in response to inflammatory and immune-mediated stress. Its unique position at the intersection of vascular biology, inflammation, and immune dysregulation aligns closely with the pathophysiology of pediatric lupus. Evidence from adult lupus studies, supported by pediatric data from other inflammatory conditions, suggests that endocan may serve as an early indicator of subclinical vascular dysfunction, complementing traditional endothelial markers and noninvasive vascular imaging techniques.

From a pediatric perspective, the potential value of endocan lies in its ability to identify children with lupus who are at heightened vascular risk long before clinical cardiovascular disease becomes apparent. When integrated into a multimarker framework alongside established inflammatory, renal, and endothelial indicators, endocan could enhance early risk stratification, inform monitoring strategies, and guide timely preventive interventions. However, important gaps remain, particularly regarding pediatric-specific reference ranges, the influence of growth and pubertal development, and the longitudinal behavior of endocan across disease flares and remission.

Future research should prioritize well-designed pediatric studies that validate endocan against functional and structural vascular endpoints, clarify its prognostic significance, and evaluate its responsiveness to therapeutic interventions. Addressing these gaps will be essential for translating endocan from a promising research biomarker into a clinically meaningful tool for improving long-term cardiovascular outcomes in children with systemic lupus erythematosus.

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