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Regulation of eNOS (Endothelial Nitric Oxide Synthase) in Nephrotic Syndrome Pathophysiology: Literature Review

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ABSTRACT

Introduction: Nephrotic syndrome (NS) is a chronic pediatric kidney disorder marked by proteinuria, edema, and impaired renal function, with eNOS-derived nitric oxide (NO) dysregulation implicated in its pathogenesis.
Methods: This literature review analyzed studies discussing the role of eNOS in the pathogenesis of NS, particularly steroid-sensitive nephrotic syndrome (SSNS) in pediatric patients. Relevant articles were identified from scientific databases using keywords related to nephrotic syndrome, eNOS, nitric oxide, and renal dysfunction. The selected studies included experimental, genetic, and clinical investigations evaluating eNOS expression, NO production, and associated renal outcomes. Data from the included studies were synthesized narratively to identify the relationship between eNOS dysregulation and NS progression.
Results: The reviewed studies demonstrated that eNOS-derived NO is essential for renal vasodilation, sodium excretion, and blood pressure regulation. Reduced eNOS activity and decreased NO availability were associated with proteinuria, sodium retention, edema, and hypertension in NS. Several studies reported that eNOS polymorphisms, including eNOS4a/b VNTR, were linked to lower plasma NO levels and progressive glomerular injury. Experimental models of NS also showed decreased eNOS and neuronal NOS expression, resulting in impaired natriuresis and renal dysfunction.
Conclusion: Dysregulation of the eNOS–NO pathway may contribute to NS through altered sodium handling, vascular tone, and blood pressure regulation. However, evidence is heterogeneous, with urinary NO metabolites, genetic polymorphisms, and tissue eNOS expression showing inconsistent patterns. Further pediatric studies are needed to clarify the relationship between eNOS, NO bioavailability, and clinical outcomes before eNOS-directed therapies can be recommended.

Keywords: Nephrotic syndrome; endothelial Nitric Oxide Synthase; vasodilation; blood pressure; endothelial cell

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Introduction

High salt retention and the development of edema are the features of nephrotic syndrome (NS). Fluid moves from the intravascular compartment to the interstitial space and plasma volume decreases as a result of this condition, which is related to a decrease in plasma albumin levels (plasma oncotic pressure). Decreased intravascular volume is estimated to cause the renal tubules to reabsorb water and salt by activating the renin-angiotensin-aldosterone sequence, increasing sympathetic response, and increase vasopressin, and preventing the synthesis of atrial natriuretic peptide. Due to inherent abnormalities in tubular sodium transport and renal hemodynamics that are incompatible with hypoalbuminemia and hypovolemia, this concept is currently under the discussion.[1,2]

Humans and mice with congenital analbuminaemia typically have an absence of edema. Additionally, patients with nephrotic syndrome typically have normal or elevated plasma volume. Furthermore, intravascular volume depletion in nephrotic syndrome has not consistently been demonstrated by reassuring functional plasma indicators, such as hematocrit or plasma concentrations of renin, vasopressin, norepinephrine, aldosterone, and atrial natriuretic peptide. In fact, patients with nephrotic syndrome typically have normal levels of atrial natriuretic peptide, vasopressin, and norepinephrine, but decreased levels of renin activity and aldosterone. Another study showed that natriuresis triggers an increase in levels of serum albumin in individuals with nephrotic that establish remission with steroid, and notably, aldosterone and plasma renin activity increase as edema resolves.[1,2,3]

Nitric oxide (NO) is a messenger molecule that regulates several biological processes and is present in many different places. Nitric oxide is created by the stereospecific oxidation of L-arginine by a group of enzymes known as nitric oxide synthases (NOS). Nitric oxide synthases (NOS) are a class of enzymes that produce nitric oxide through the stereospecific oxidation of L-arginine. NOS has three specific isoforms: NOS I or neuronal NOS (nNOS), NOS II or inducible NOS (iNOS), and NOS III or endothelial NOS (eNOS). Vasodilatory tone, which is sustained by the stimulating release of NO from eNOS-iNOS in systemic and renal arteries, controls blood pressure, tissue perfusion, and renal and vascular system resistance. Furthermore, intrarenal NO regulates as an endogenous diuretic by acting as primary regulator of water and sodium excretion by the renal system. By preventing sodium reabsorption, NO produced in tubular epithelial cells by iNOS stimulates natriuresis. Additionally, NO produced by nNOS in the macula densa reduces afferent arteriolar vasoconstriction associated with tubuloglomerular feedback in response to changes in Na concentration in the lumen, promoting glomerular filtration and Na excretion.[4,5,6]

eNOS has been the subject of ongoing research, but its specific contribution to nephrotic syndrome remains incompletely defined. Previous studies have reported reduced renal NOS expression in experimental nephrotic syndrome, increased urinary NO metabolites in children with minimal change nephrotic syndrome, and associations between eNOS gene polymorphisms and susceptibility to nephrotic syndrome. However, these findings do not consistently establish whether altered eNOS expression or activity leads to reduced NO

bioavailability and impaired natriuresis, or whether increased urinary NO metabolites represent a compensatory response or increased NO production from other NOS isoforms. Furthermore, the relationship between eNOS-related abnormalities and clinical outcomes such as sodium retention, edema, hypertension, proteinuria, and disease relapse remains uncertain, particularly in children with nephrotic syndrome. Therefore, this review aims to synthesize the available experimental, genetic, and clinical evidence regarding eNOS expression and activity, NO bioavailability and urinary NO metabolites, eNOS genetic polymorphisms, and their associations with the pathophysiology and potential therapeutic implications of nephrotic syndrome.

Nephrotic Syndrome

Protein leaking from the circulation into the urine through damaged glomeruli is the hallmark of NS. This syndrome is defined by proteinuria (≥40 mg/m²/hour or urine protein-to-creatinine ratio ≥200 mg/mg or 3+ protein on urine test), hypoalbuminemia (<25 g/L), and edema. The Consensus of Idiopathic Nephrotic Syndrome in Children issued by the Indonesian Pediatric Society (IDAI) explains that the diagnostic criteria for NS are massive proteinuria, hypoalbuminemia, edema, and may be accompanied by hypercholesterolemia.[7]

Congenital SN in children might manifest during their early three months of life, and is typically caused by genetic abnormalities that impact the glomerular basement membrane or podocytes, while it is rarely linked to congenital infections. Nephrotic nephrosis can be caused by a wide range of underlying etiologies in addition to the congenital form of SN, such as glomerular diseases, vasculitis, infections, poisons, cancers, genetic abnormalities, and, most frequently, unidentified reasons. Children with SN should be treated in hospital for the purpose of diagnosis, evaluation and dietary management, edema management, initiation of steroid treatment, and education of parents. Before treating children with SN, anthropometric measurements should be taken to assess nutritional status and blood pressure, check for signs of systemic diseases such as lupus, and look for foci of infection.[3,7]

Nitric Oxide And eNOS

The short-lived gaseous free radical nitric oxide (NO) has been considered an air contaminant. The nitric oxide synthase (NOS) family is the most investigated and possibly most important biological generator of NO and this enzyme produces NO by oxidizing l-arginine. NOS enzymes have relevance in several physiological contexts, according to biochemical, genetic, and phylogenetic investigations. There are three specific NOS isoforms found in mammals: neuronal (nNOS or NOS I), inducible (iNOS or NOS II), and endothelial (eNOS or NOS III).[8,9,10]

Neurons, skeletal muscle, and renal macula densa all constitutively express nNOS (NOS1), which produces low amounts of NO in a calcium/calmodulin-dependent way to mediate neurotransmission, synaptic plasticity, and tubuloglomerular feedback for GFR regulation. Cytokines and LPS induce iNOS expression in

macrophages and inflammatory tissues, resulting in high sustained NO without the need for calcium to support inflammation, pathogen destruction, and immunological defense. In vascular endothelial cells and kidney glomeruli, eNOS (NOS3) is constitutively active. It produces tonic low NO through calcium, shear stress and phosphorylation to control blood pressure, vasodilation, platelet aggregation, and renal natriuresis.[11,12]

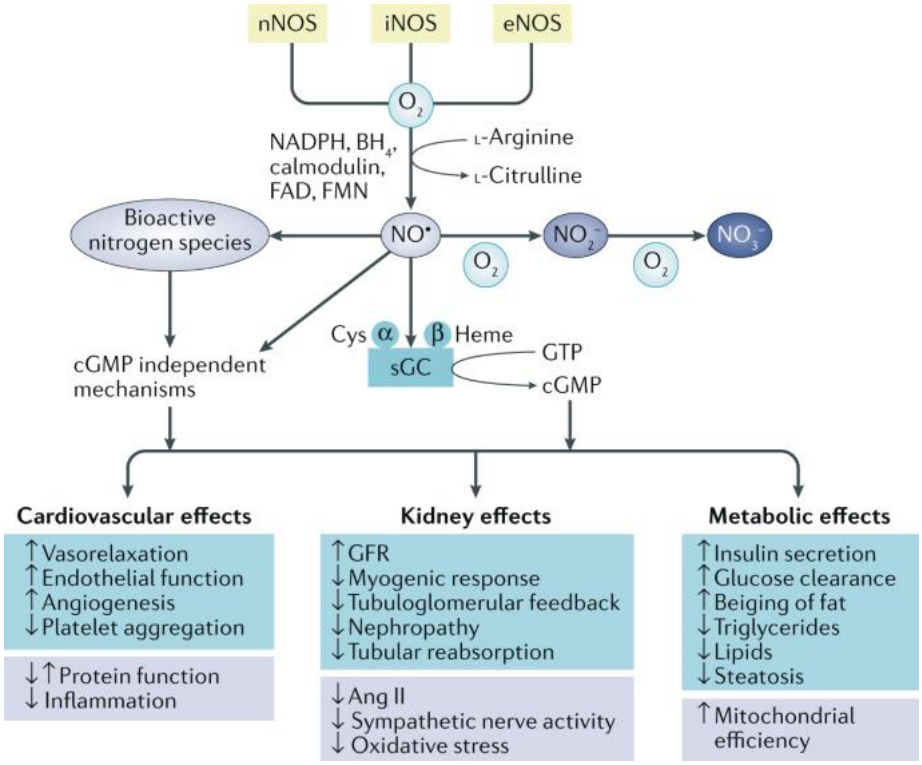

Figure 1. The role of nitric oxide (NO). The NO pathway and possible effects of NO on cardiovascular, renal, and metabolic systems[10]

The oxygenase/reductase enzymes of Nitric Oxide Synthase (NOS) (nNOS, iNOS, and eNOS) utilize NADPH, BH4 (tetrahydrobiopterin), FAD, FMN, calmodulin, heme, and O to transform L-arginine into bioactive NO and L-citrulline. Without the involvement of the NOS system, other pathways produce reactive oxygen/nitrogen species (O_2, NO_2, $ONOO^-$), including NO. Both cGMP-dependent and cGMP-independent processes are linked to signaling through these nitrogen species. NO has the following effects in the kidney: prevents tubular salt reabsorption, reduces tubuloglomerular feedback, and maintains the glomerular filtration rate.[10,11,12]

Quantitative comparison (rough peak levels): iNOS > nNOS > eNOS. eNOS produces the lowest tonic NO (picomolar range) for precise vascular homeostasis; this situation is strictly regulated by shear stress, phosphorylation, and nitrogen storage in caveolae, ensuring brief physiological bursts during vasodilation without causing tissue damage. While iNOS produces high-output responses, nNOS/eNOS provides physiological signaling; all catalyze L-arginine to NO and L-citrulline, although their functions distinct in subcellular targeting and mechanism of action. [11,12]

The presence of nNOS in the macula densa and eNOS in the renal blood vessels has been repeatedly reported; other studies reveal eNOS expression in tubular epithelial cells. The majority of nephron segments, including the proximal tubule, thick ascending limb of the loop of Henle, macula densa, distal tubule, and collecting duct, have been reported to express nNOS protein and mRNA in healthy human kidney tissue samples. Only the endothelium expressed eNOS and enzyme activity tests verified revealed the cortex has higher levels of NOS expression than the medulla.[13,14]

The kidney expresses all of three specific NOS isoforms (nNOS, iNOS, and eNOS) constitutively. eNOS expression is high in the endothelial layer of arterioles and renal capillaries and in the epithelial cells of the collecting ducts, while nNOS expression is high in the macula densa but lower in intrarenal neurons, efferent arterioles, thick epithelial cells of the ascending limb, and mesangial cells. Interstitial mesangial cells, medullary cells, vascular smooth muscle cells, and epithelial cells in the thick ascending limb, proximal tubule, and collecting duct also express iNOS. A specific decrease in eNOS expression in NS disrupts low-level renal NO production, causing sodium retention despite normal iNOS/nNOS expression. [11,12,14]

There remains a controversy on NO's precise function in kidney disease. NO metabolite levels in urine were higher in SRNS than in SSNS. NO metabolite levels in urine increased 3.0 times in SSNS and 4.2 times in SRNS relapse group in comparison with the control population. Urinary NO metabolites persisted to be elevated in both groups during remission. According to another report, children with minimal change nephrotic syndrome excreted higher nitrite in their urine, a stable product of NO. It is uncertain how elevated urine nitrite excretion contributes to the disease's clinical symptoms in the children in this group. Considering there were no differences between patients with focal segmental glomerulosclerosis and control subjects, elevated urine nitrite excretion in Minimal-Change nephrotic syndrome cannot be linked to the nephrotic syndrome itself. The persistent rise in nitrite excretion during relapse and remission raises the possibility that renal NO production contributes to minimal-change nephrotic syndrome rather than modulating proteinuria.[13,14]

Immunological and Genetic Disorders Associated with Nephrotic Syndrome

SSNS patients may have challenging to manage steroid dependence and/or frequent relapses (SDNS/FRNS). Significant morbidity, treatment failure, and recurrent relapses are frequently caused by infections. Randomized clinical trials have shown that levamisole keeps FRNS patients from relapsing and increases their relapse-free period. Classical HLA class II molecules are highly polymorphic heterodimeric transmembrane proteins which are encoded by the HLA-II gene on chromosome 6. A crucial stage in the development of particular CD4+T cells in the adaptive immune response is the presentation of foreign antigens in HLA class II molecules by professional antigen-presenting cells. This mechanism of antigen processing and presentation is strongly associated with bacterial or viral infections.[15,16,17]

The "a" allele of eNOS4 is strongly linked to lower plasma NO levels. The pathophysiology of human

glomerular disease may involve the eNOS4 a/b tandem repeat number variation (VNTR) polymorphism, which is regarded as a risk factor for progressive kidney disease. Decreased eNOS expression in lupus nephritis and IgA nephropathy patients, suggesting a decrease in eNOS's physiological effects on injured glomeruli. Recent studies have correlated increased NO generation to hyperfiltration and microalbuminuria, two characteristics of Diabetic kidney disease in its early stages. An experimental study showed an increase in intrarenal nNOS production in rats with chronic diabetes, which is an important mechanism in the development of renal hyperfiltration in diabetes. This may be due to suppression of the tubuloglomerular feedback system as a result of excessive nNOS synthesis in the kidneys.[5,10,18, 19, 20]

Recurrence of SSNS is characterized by the recurrence of proteinuria. The recurrence rate is 60%; though this is depends upon the severity of steroid treatment. The number of recurrences within the first six months following diagnosis is a reliable indicator that the disease might progress further. Based on recent studies, there is no noticeable rise in the frequency of the aa and ab genotypes or alleles in individuals who have more relapses. These findings suggest that the eNOS4 genotype and the recurrence rate in SSNS patients are unrelated.[3,20]

Table 1. Research related to eNOS in Nephrotic Syndrome

Author, Year	Study Type	Sample / Participants	Population	Main outcomes measured	Main findings	Statistical significance	Main limitation
Ni *et al, 2003*	Review Article	Rats; n=6 per experimental group	PAN-induced nephrotic syndrome; protein-overload proteinuria; inherited analbuminemia	Urinary NO metabolites, fractional Na excretion, renal iNOS/nNOS/eNOS expression, blood pressure	PAN-induced NS showed reduced fractional Na excretion and reduced renal NOS expression, particularly iNOS and nNOS, with reduced urinary NOx. Proteinuria appeared to be an important mediator of NOS downregulation.	$p<0.01$ for fractional Na excretion versus controls	Animal model; findings may not be directly generalizable to human pediatric NS.
Bae *et a, 2010l*	Experimental	PAN-induced NS rats; n=8/group for major experimental comparisons	Experimental PAN-induced NS	Urinary Na excretion, Na balance, renal nNOS/eNOS/iNOS expression, urinary NOx, ET-1/ETB receptor	On day 7, nNOS expression and urinary NOx were decreased with sodium retention; nNOS recovered and urinary NOx increased by day 14. eNOS expression did not significantly differ between groups.	nNOS reduction: $p<0.05$; urinary NOx changes: $p<0.05$	Experimental animal study; eNOS was not significantly altered, limiting direct conclusions about eNOS.

Ray *et al, 2015*	Review Article	Not applicable	Nephrotic syndrome	Urinary nitrite excretion	Review supports multifactorial sodium retention in NS, including activation of ENaC by filtered proteases; it provides indirect mechanistic context for NO-related sodium handling.	Not applicable	Review article; does not provide original effect estimates and does not specifically evaluate eNOS.
Ciuntu *et al, 2016*	Cohort	25 SSNS, 20 SRNS, 20 mixed CGN	Pediatric SSNS and SRNS	eNOS Glu298Asp and nNOS C276T polymorphisms	Urinary NO metabolites increased approximately 3.0-fold in SSNS and 4.2-fold in SRNS during relapse versus controls and remained elevated during remission.	Reported as statistically significant in the original study	Small sample size; heterogeneous disease groups; NO metabolites are indirect measures of NO production.
Elmougy R, 2021	Case Control	98 children with NS and 101 controls	Pediatric NS	eNOS 27-bp VNTR, GSTP1 and IL-10 polymorphisms	eNOS 27-bp VNTR genotype distribution differed between NS and controls. AB and BB genotypes were less frequent in patients: AB 17.2% vs 22.8% (OR 0.19, 95% CI 0.06–0.58) and BB 54.7% vs 70.3% (OR 0.19, 95% CI 0.07–0.50).	AB p=0.0026; BB p=0.0004	Genetic association does not establish causality or demonstrate altered eNOS expression/function.
Niepolski *et al, 2024*	Cohort	50 hemodialysis patients and 26 healthy controls	ESRD on hemodialysis; not NS-specific	Plasma eNOS, phosphorus, blood pressure	Plasma eNOS was lower in HD patients than controls (0.725 vs 1.46 ng/mL); higher BP was associated with lower plasma eNOS in patients with dyslipidemia.	eNOS comparison p=0.004; phosphorus/eNOS analyses p<0.05	Indirect evidence because participants had ESRD on hemodialysis rather than nephrotic syndrome.

Result

Twenty-one sources were reviewed, comprising narrative review articles, experimental animal studies, cohort studies, and a case-control study, focusing on the role of eNOS and nitric oxide in the pathophysiology of nephrotic syndrome (NS) (Table 1). A consistent pattern emerged: impaired eNOS activity or expression accompanies sodium retention, hypertension, and glomerular damage in NS. Both nNOS and eNOS expression decreased during active proteinuria in the puromycin aminonucleoside model, which hindered renal sodium excretion. Interestingly, restoring nNOS and upregulating renal endothelin receptor type B in later stages of the disease improved natriuresis, in line with previous biochemical research that linked NOS downregulation to the severity of proteinuria in NS [11,17,20].

Clinical and mechanistic reviews converged on sodium retention and hypertension as the principal downstream consequences of reduced eNOS-derived NO, disrupting tubuloglomerular feedback and permitting inappropriate tubular sodium reabsorption, alongside a complementary pathway in which filtered serum proteases directly activate epithelial sodium channels (ENaC)[14]. A cohort study of urinary NO metabolites found higher excretion in steroid-resistant NS (SRNS) than steroid-sensitive NS (SSNS)[20]. This pattern appears to be at odds with lower tissue eNOS expression reported elsewhere.

Genetic association studies identified the eNOS4 a/b variable number tandem repeat (VNTR) polymorphism as a recurrent risk marker, with the eNOS4 "a" allele linked to lower plasma NO and the eNOS 27-bp VNTR genotype proposed as a candidate marker for early NS prediction[19]; related polymorphism studies reported associations with NS risk in children[1] and with minimal change NS without a clear relationship to relapse frequency, while a comparable eNOS polymorphism (Glu298Asp) has independently been associated with diabetic nephropathy susceptibility [6, 13,21,21]. The eNOS–hypertension link was extended to systemic blood pressure regulation in advanced kidney disease as a cohort of dialysis patients revealed that lower circulating eNOS concentrations were correlated with increased systolic and diastolic blood pressure [5].

Discussion

These findings converge on eNOS as an active contributor to the sodium retention and hypertension that define NS, rather than a bystander. Under physiological conditions eNOS-derived NO acts as an endogenous diuretic that limits tubular sodium reabsorption and modulates tubuloglomerular feedback; when eNOS activity falls, as shown experimentally and inferred from proteinuria-associated NOS downregulation in humans, this natriuretic brake is lost. This mechanism operates alongside, rather than instead of, protease-mediated ENaC activation, indicating that NS-associated sodium retention is multifactorial. The persistent elevation of urinary NO metabolites despite reduced tissue eNOS expression is reconcilable if compensatory iNOS upregulation in injured tissue offsets the eNOS deficit at the level of total urinary output, or if oxidative stress diverts NO toward peroxynitrite formation, so that elevated NO generation coexists with reduced bioavailable, functional NO [8-12,20]. Under either explanation, urinary NO metabolite concentration alone is an unreliable proxy for eNOS activity and should not be read as evidence against a role for eNOS dysfunction in NS.

The genetic data add a further layer of interpretation. The eNOS4 a/b VNTR and Glu298Asp variants recur across NS, IgA nephropathy, lupus nephritis, and diabetic nephropathy, suggesting a shared genetic susceptibility pathway across glomerular diseases rather than one specific to NS [1,6,13,18]. However, the absence of a consistent association between eNOS4 genotype and relapse frequency in SSNS indicates that eNOS genetic variation may influence susceptibility to disease onset or sodium-retentive complications without determining steroid-responsiveness or relapse behavior, so eNOS genotyping is unlikely to replace existing relapse-prediction markers but could still help identify children at elevated risk of hypertension or progressive kidney injury [20]. The dialysis-cohort association between lower circulating eNOS and higher blood pressure, taken together with the endothelial and thrombotic consequences of NS-associated endothelial injury, points to eNOS as a mechanistic bridge between glomerular protein leak, endothelial dysfunction, and cardiovascular risk across the course of NS, not solely a determinant of acute edema [4,5].

These conclusions should be weighed against a fragmented evidence base: much of the mechanistic support rests on a single experimental model and on narrative reviews rather than original human data, the identified clinical studies are heterogeneous in design and NS subtype, and few were conducted specifically in pediatric populations despite SSNS being predominantly a childhood disease [7,8,12,14,17]. No reviewed study combined eNOS4 genotyping, tissue or plasma eNOS measurement, and urinary NO metabolites within the same pediatric cohort. Prospective pediatric studies that pair these measures with longitudinal sodium balance and blood pressure data, together with mechanistic work distinguishing eNOS- from iNOS-derived urinary NO, would clarify these relationships; and given the natriuretic and vasodilatory actions of eNOS-derived NO, interventions that restore eNOS activity or NO bioavailability, such as L-arginine or tetrahydrobiopterin supplementation, antioxidant strategies limiting peroxynitrite formation, or agents upregulating endothelial NOS expression, warrant evaluation as adjunctive approaches to managing edema, relapse, and long-term cardiovascular risk in children with NS [8-10,12].

Conclusion

Overall, the available evidence indicates that dysregulation of the eNOS–NO pathway may contribute to the pathophysiology of nephrotic syndrome, particularly through altered renal sodium handling, natriuresis, vascular tone, and blood pressure regulation. Experimental studies support reduced NOS-related signaling in nephrotic syndrome, while clinical studies demonstrate increased urinary NO metabolites and genetic associations involving eNOS polymorphisms. However, these findings are heterogeneous and do not establish a consistent relationship between tissue eNOS expression, NO bioavailability, urinary NO metabolites, and clinical disease activity. Importantly, urinary NO metabolites should not be considered a direct surrogate of eNOS activity because they may reflect NO generated by multiple NOS isoforms and compensatory mechanisms. Therefore, eNOS represents a plausible mechanistic and potential therapeutic target in nephrotic syndrome, but further well-designed pediatric studies integrating eNOS expression or activity, NO bioavailability, genetic variants, urinary NO metabolites, sodium balance, blood pressure, and clinical outcomes are required before eNOS-directed therapy can be recommended.

Conflict of Interest

No conflict of interest exists.

Acknowledgments

None declare

List of Abbreviations

NS: Nephrotic Syndrome; NOS: Nitric Oxide Synthase; SSNS: Steroid-Sensitive NS; eNOS: endothelial NOS; SDNS/FRNS: Steroid Dependence and/or Frequent Relapses Nephrotic Syndrome; ENaC: Epithelial Na Channels.

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