



Review

# The View of Pediatric Nephrotic Syndrome as a Podocytopathy

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**Abstract:** Nephrotic syndrome (NS) is a complex clinical entity characterized by proteinuria, hypoalbuminemia, and edema. In this review, we propose the view of NS as a podocytopathy, highlighting the importance of understanding the role of podocytes in the development of this condition. We discuss the various etiologies of NS, ranging from congenital to primary renal diseases, as well as secondary forms due to systemic diseases. We also delve into the mechanisms underlying podocyte injury, which plays a crucial role in the development of NS. By viewing NS as a podocytopathy, we suggest potential implications for the diagnosis and treatment of this condition, including the use of podocyte-specific biomarkers and targeted therapies. Our review provides a comprehensive overview of NS and its underlying mechanisms, emphasizing the importance of a multidisciplinary approach to the diagnosis and management of this condition. Further research is essential to better understand the complex interplay between podocyte injury and the development of NS, with the ultimate goal of improving patient outcomes.

**Keywords:** nephrotic syndrome; podocyte; proteinuria; glomerular filtration barrier; biomarkers



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## 1. Introduction

Nephrotic syndrome (NS) is a clinical entity characterized by the triad of proteinuria, hypoalbuminemia, and edema [1]. It is a group of diseases composed of numerous etiologies, ranging from congenital, such as Finnish Type Nephropathy and Diffuse Mesangial Sclerosis, to primary renal diseases, including Minimal Change Nephrotic Syndrome (MCNS) and Focal Segmental Glomerulosclerosis (FSGS), or secondary forms due to systemic diseases such as, for instance, diabetes mellitus and lupus erythematosus [2]. The reported incidence of childhood NS is 2–7 per 100,000 children, with a prevalence of about 16 cases per 100,000 and variability among ethnic groups. The peak age of onset of childhood NS occurs at 2–3 years in most cases [3]. MCNS is the most common histological variant, accounting for approximately 80% of NS cases in children, followed by FSGS, which, although less common, is more related to poor long-term outcomes [4,5].

The main pathophysiological alteration in NS is the impairment of the glomerular filtration barrier. Therefore, its permeability becomes non-selective, and urinary protein loss occurs. All components of the glomerular barrier may interfere with the permeability of molecules. These components include the fenestrated endothelium, the glomerular basement membrane (GBM), and the podocytes. In NS patients, the effacement of the foot processes of the podocytes is a common finding in the electronic microscopy of the kidney tissue [6]. Podocytes are highly differentiated epithelial cells with a large cell body and elongated cellular extensions, the foot processes, that interdigitate along the outer wall of the glomerular capillary and, among other functions, provide structural support and control the filtration process [7].

Being the final barrier to protein loss in the glomerulus, alterations in podocyte structure can explain why injuries in these cells, such as the effacement of their foot

processes, are typically related to proteinuria and hypoalbuminemia and, therefore, to the conditions under the NS umbrella [6]. In this context, this review aims to summarize the current understanding of NS as a podocytopathy and to discuss the main molecular, genetic, and histological markers and their influence on the onset and outcome of the disease.

## 2. Pathophysiological Mechanisms of the Podocytopathies

### 2.1. Pathophysiology of Nephrotic Syndrome and the Glomerular Filtration

Despite often occurring rapidly, NS can have an insidious presentation, with proteinuria before the onset of symptoms. The proteinuria indicates an altered permeability of the glomerular filtration barrier [8] and contributes to edema and hypoalbuminemia. Hypoalbuminemia induces lipoprotein synthesis, which causes hyperlipidemia [2,3]. The three components of the glomerular filtration barrier—the fenestrated endothelium, the GBM, and the podocytes—control the size of filtered molecules [9]. The podocytes are visceral glomerular epithelial cells, and their injury plays an important role in the development of the NS. Therefore, the main pathophysiological alterations in NS justify the view of this syndrome as a podocytopathy [2].

Podocytes are highly specialized and polarized epithelial cells related to the synthesis of extracellular matrix components of the GBM. Furthermore, these cells have a structural role in supporting the glomerular capillaries with their interdigitating foot processes (FP), which are linked to each other through a special cell–cell junction, the slit diaphragm (SD). The podocyte also synthesizes many proteins from the SD. The unique zipper-like architecture of the SD is essential to the glomerulus permeability; therefore, podocyte depletion due to detachment, apoptosis, or necrosis is a critical step in the development of NS [7].

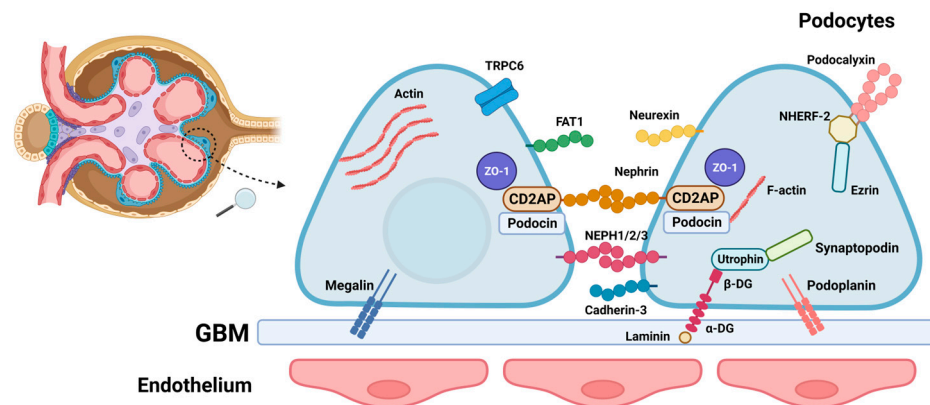
Electron microscopy shows the effacement of the foot processes as a major factor related to the glomerular lesion [7]. The podocytes and the SD zipper-like array are composed of an extensive group of molecules, including an actin cytoskeleton and proteins such as ZO-1, nephrin, podocin, and CD2AP, in both the podocyte itself and the GBM. Some etiologies of congenital and steroid-resistant NS can be linked to mutations in genes encoding some of these components, altering the glomerular filtration barrier and leading to intense urinary protein loss [1].

The mechanisms that underlie FP effacement and podocytes' response to injury are important to determine the clinical manifestations of NS and prognosis [6]. Furthermore, the understanding of podocyte-specific protein alterations and the dynamic changes of glomerular permeability and selectivity are also relevant for the management and treatment of NS [2,3].

### 2.2. Podocyte Foot Processes: Update on Molecular Anatomy and Effacement

Each podocyte FP contains a contractile system composed of actin, myosin-II, actinin-4, talin, and vinculin [10]. The cytoskeleton molecular composition in podocyte FP is critical to podocyte function and effacement processes. The foot processes (FPs) are anchored to the GBM because of 31 integrin complexes, which, consisting of heterodimeric transmembrane receptors, mediate cell attachment to the extracellular matrix and are crucial for cell signaling. The adjacent FPs of the same podocyte are bundled using actin filaments, which form arches between these adjacent FPs. The connection between neighboring FPs is the SD [6].

The SD is the main size-selective filter barrier in the kidney. The protein composition of SD justifies the importance of this cellular junction for glomerulus permeability. The main proteins of the SD are nephrin, P-cadherin, CD2AP, ZO-1, FAT, podocin, and Neph1 (Figure 1). These contractile proteins allow the maintenance of glomerular filtration and also indicate that the fusion of podocyte FPs and the obliteration of SD are highly related to their alterations, leading to NS [6,11].



**Figure 1.** Schematic representation of the glomerular slit diaphragm, a pivotal structure within the glomerulus that is essential for the filtration barrier's integrity. Positioned between podocyte foot processes and the glomerular basement membrane (GBM), this intricate assembly involves a network of molecules crucial for maintaining structural and functional integrity. Key components include transmembrane proteins like nephrin (a structural protein forming the backbone of the slit diaphragm), podocin (interacting with nephrin, crucial for slit diaphragm function), NEPH1/2/3 (members of the neph family proteins contributing to slit diaphragm molecular architecture), Cadherin 3 (involved in cell adhesion within podocytes), and podoplanin (a transmembrane protein expressed in podocytes). Additionally, molecules such as laminin (a component of the GBM providing structural support) and dystroglycan complex proteins ( $\alpha$ -DG,  $\beta$ -DG) (linking the cytoskeleton to the extracellular matrix) are integral to the GBM. The schema also highlights other essential players, including utrophin (participating in cytoskeletal organization), synaptopodin (involved in actin cytoskeleton regulation), ezrin (linking actin filaments to the plasma membrane), NHERF-2 (a scaffold protein interacting with nephrin and podocin), podocalyxin (a sialoprotein contributing to the glycocalyx), FAT1 (a cell adhesion and signaling protein), ZO-1 (a tight junction-associated protein), TRCP6 (an ion channel implicated in slit diaphragm function), actin (a cytoskeletal component crucial for podocyte structure), and megalin (a receptor involved in protein reabsorption in the proximal tubule).

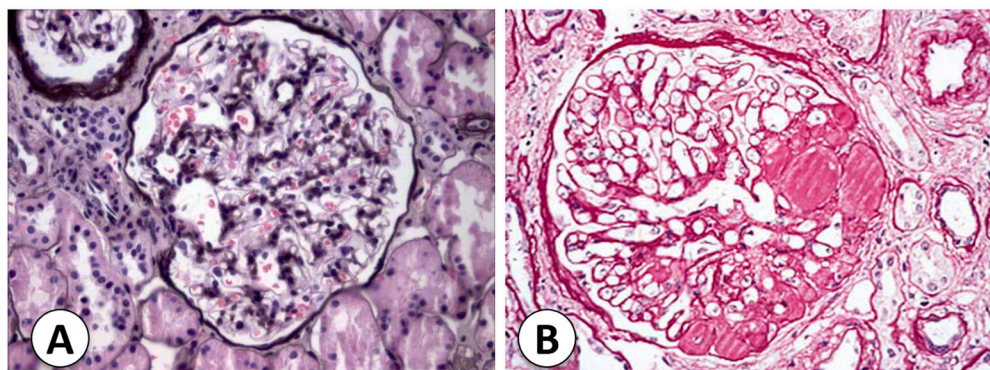
There is another important protein associated with actin microfilaments in FPs, synaptopodin [12], and its expression can indicate alterations in podocytes and also in the response to therapy in many forms of NS [13]. Therefore, synaptopodin likely plays an important role in the podocyte FP molecular composition, interacting with membrane-associated guanylate kinase, WW, and PDZ domain-containing protein 1 (MAGI-1) such as actinin-4 [14]. This may indicate an association between its expression and alterations in the podocyte.

As mentioned, the molecular composition of the cytoskeleton in podocyte FPs is dynamic and determines the maintenance of glomerular filtration. This has been demonstrated by using the acute protamine sulfate (PS)/heparin perfusion model, which dramatically reduces FPs in rodents [15,16]. Interference with one of the three membrane domains of the basolateral portion of FPs, including the apical membrane domain, the SD complex, and the basal membrane domain, can lead to alterations in the actin cytoskeleton. The consequences of these alterations are the fusion and effacement of podocyte FPs and the obliteration of the SD.

### 2.3. Histopathology of Common Types of Nephrotic Syndrome in Childhood

The types and causes of NS in childhood vary according to age. The most frequent type of NS in pediatric patients is primary or idiopathic disease, in which the etiology is not defined. When the NS starts before 1 year of age, the possibility of congenital NS should be considered, mostly in cases that occur before 6 months of age. Congenital NS is related to mutations in proteins related to SD. When nephrotic syndrome first appears during the school-age or adolescent years, it is important to consider the possibility of secondary NS due to systemic diseases [17]. The two most common histological forms of primary NS are

MCNS and FSGS (Figure 2). Understanding histopathology is important to guide correct molecular and morphologic diagnoses and posterior management of NS [18].



**Figure 2.** Histological comparison of Minimal Change Nephrotic Syndrome (MCNS) and Focal Segmental Glomerulosclerosis (FSGS). (A) Representative histological slide of kidney tissue from a patient diagnosed with Minimal Change Nephrotic Syndrome (MCNS). The glomerulus exhibits minimal structural alterations, characterized by a lack of significant changes in the glomerular basement membrane, mesangium, and podocytes (Jones silver stain). Electronic microscopy can reveal diffuse effacement of podocyte foot processes, a hallmark feature of MCNS. (B) In contrast, kidney tissue from a patient diagnosed with Focal Segmental Glomerulosclerosis (FSGS) is depicted in this section (h&E staining). The histological examination reveals focal and segmental areas of sclerosis within the glomerulus, indicating regions of glomerular injury and scarring. The presence of hyalinosis, adhesions, and segmental obliteration of capillary lumina is evident, reflecting the characteristic histopathological changes associated with FSGS. Both micrographs were captured at a magnification of 400 $\times$  (personal archive of the authors).

### 2.3.1. Congenital Nephrotic Syndrome (Finnish Type)

This form of NS is highly related to prematurity in neonatal and prenatal presentations as well. In Finland, the incidence reaches 1:8200 births and is an autosomal-recessive disorder with heavy proteinuria in the neonatal period. The Finnish nephropathy gene is located on the long arm of chromosome 19 (19q13.1), which codes for nephrin [2]. The Finnish nephropathy gene is located on the long arm of chromosome 19 (19q13.1), which codes for nephrin. Around 70 changes to nephrin have been found in different parts of the body. These changes can be single nucleotide missense mutations, splices, insertions, deletions, or nonsense. Some mutations, such as Fin-major (deletion in exon 2) and Fin-minor (nonsense mutation in exon 26), are the most common. The kidney histopathology may help with congenital NS diagnosis, especially by using electron microscopy and immunohistochemistry [18]. A renal biopsy shows many glomeruli with mesangial hypercellularity and hyperlobulated capillary tufts. Furthermore, proximal and distal tubules may present microcystic dilatation, and the podocytes present FP effacement and/or villous transformations under electron microscopy. Immunohistochemical staining for nephrin is an important method to differentiate FN from other causes of congenital NS [2].

### 2.3.2. Diffuse Mesangial Sclerosis

The presentation of diffuse mesangial sclerosis (DMS) is similar to that of FN. However, its presentation can be later, up to 4 years of age, but usually persistent NS is described within the first 9 months of life. DMS is the second-most common cause of congenital NS. [1] The glomerular phenotype of the disease is associated with other disorders, such as Galloway–Mowat syndrome, Pierson syndrome, Frasier syndrome, and others. The pathology of the kidneys displays prominent, closely spaced podocytes in the early stages, and the glomeruli might be enlarged and exhibit hyaline casts. In immunofluorescence, nonspecific mesangial IgM, C3, and C1q deposits are found, while electron microscopy also shows podocyte hypertrophy and irregular FP effacement. In the late stages of DMS,



the glomeruli are damaged and have thickened capillary loops, smaller capillary lumens, and a sclerotic mass in the mesangium [18].

### 2.3.3. Focal Segmental Glomerular Sclerosis

Focal segmental glomerular sclerosis (FSGS) is responsible for 10 to 20% of NS cases in children [2]. The podocyte is the main site of injury in FSGS. The damage occurs through a variety of mechanisms, including immune, toxic, and viral, mechanical injuries, and genetic dysfunction [19]. Injured podocytes are missed in the urinary space, resulting in podocyte effacement. The remaining podocytes hypertrophy and cover the glomerular capillary surface in response to this lack of podocytes. Intracapillary hypertension can cause damage to podocytes and endothelial cells. It can also cause changes in the mesangial cells that lead to sclerosis [20].

In primary FSGS, a circulating factor may be involved in the pathophysiology of NS. It is probably associated with some cytokines that disturb podocyte function [21]; therefore, it can reoccur after kidney transplantation [22]. In fact, the recurrence of idiopathic FSGS occurs in around one-third of patients after transplant [23]. Some molecules have been associated with the recurrence of FSGS, including cardiotrophin-like cytokine factor 1 [24], apoA1b (an isoform of ApoA1) [25], anti-CD40 antibody [26], and serum urine-type plasminogen activator receptor (suPAR) [27]. The association with suPAR is still controversial [28]. However, up to now, no molecule has been definitively established as the circulating factor in all cases of primary FSGS.

More than 50 genes have been presented as potential factors for monogenic forms of FSGS. The group of genes includes those involved in slit diaphragm structure, actin cytoskeleton, and cell-signaling apparatus [29,30]. FSGS can also be drug-induced, as IFN- $\alpha$ , - $\beta$ , or - $\gamma$  therapy has been linked to the occurrence of collapsing glomerulopathy in a case series of 11 subjects [31]. Anabolic steroid abuse has also been related to the development of FSGS. The association may be due to a combination of a direct nephrotoxic effect and adaptive glomerular changes to the increased lean body mass [32].

## 2.4. Histological Classifications for Focal Segmental Glomerular Sclerosis

### 2.4.1. Cellular Focal Segmental Glomerular Sclerosis

The description of this variant resembles focal proliferative glomerulonephritis (Table 1). On light microscopy, segmental hypercellularity and endocapillary proliferation are reported, with a luminal obliteration of capillaries [2]. Severe FP effacement is also common but with intact basement membranes [2,7]. Furthermore, there is an increase in mesangial and inflammatory cells such as neutrophils, foam cells, and monocytes. Although this variant shows marked podocyte hyperplasia [2], it is the least common one and is thought to be an early stage in the evolution of sclerotic lesions [7].

### 2.4.2. Primary Focal Segmental Glomerular Sclerosis with Mesangial Hypercellularity

This variant of FSGS reveals mainly mesangial hypercellularity in the non-sclerotic glomeruli, including the presence of IgM and C3 in these glomeruli on immunofluorescence patterns. Electron microscopy shows the classic segmental sclerosing lesions, severe FP effacement without any electron-dense deposits, and podocyte hyperplasia [2].

### 2.4.3. Familial Focal Segmental Glomerular Sclerosis

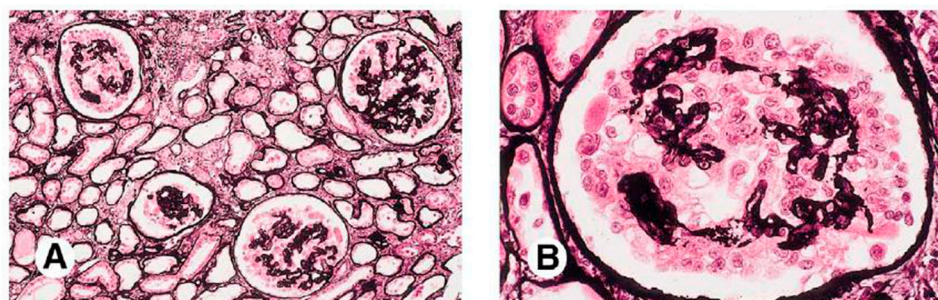
Familial FSGS is highly associated with genetic mutations, especially in genes that encode podocyte proteins [7]. Several defects in the proteins podocin (*NPHS2* gene, chromosome 1q25-31) and actinin 4 (*ACTN4*, chromosome 19q13) cause autosomal dominant FSGS [2,18]. *TRPC6* gene mutations lead to dysregulation of the cell cycle machinery with consequent apoptosis [18], while *CD2AP* mutations alter the bond between SD and the actin cytoskeleton [33]. Recent studies have shown an association between phospholipase C epsilon gene mutations (*PLCE1*, chromosome 10q23-33) and early onset NS [34]. The familial FSGS can manifest at any age and accounts for approximately 20% of FSGS cases [35].

#### 2.4.4. Secondary Focal Segmental Glomerular Sclerosis

Other diseases may also trigger FSGS in pediatric patients, including IgA nephropathy [36], hereditary nephritis (Alport's syndrome) [37], and lupus nephritis [38]. These diseases reveal different histological features, which can be traced using immunofluorescence: mesangial hypercellularity and mesangial IgA in IgA nephropathy, basement membrane abnormalities in Alport syndrome, and concurrent positive staining for IgA, IgM, IgG, C3, and C1q (full-house pattern) in lupus nephritis. Adults and children can develop secondary FSGS [2].

#### 2.4.5. Collapsing Glomerulopathy

Severe and quick loss of renal function is highly associated with collapsing glomerulopathy [18]. This variant of FSGS is characterized by an implosive collapse of the capillary loops with alterations of the basement membrane, especially its wrinkling and contraction, and hypertrophy and hyperplasia of podocytes (Figure 3) [2]. There is no mesangial sclerosis, but the proliferating visceral podocytes and parietal epithelial cells fill Bowman's space, resembling crescents (pseudocrescents) [18]. FP effacement is notorious even in glomeruli without collapsing lesions. In children, mitochondrial abnormalities have been reported to affect glomerular epithelial cells. COQ2 mutations inherited trigger an autosomal-recessive condition, which is the most common genetic variant of these mitochondrial disorders [39]. Ubiquinone replacement therapy is typical to treat this variant, and early recognition may prevent neurologic complications [18].



**Figure 3.** Histological examination of Collapsing Focal Segmental Glomerulosclerosis (cFSGS). (A) Low magnification view (100 $\times$ ) of kidney tissue depicting the characteristic features of collapsing FSGS (cFSGS). The image reveals widespread collapse and obliteration of glomerular capillaries, accompanied by prominent hyperplasia and hypertrophy of podocytes. The collapsing variant is characterized by the involvement of the entire glomerulus, leading to marked changes in the glomerular architecture. (B) Higher magnification (400 $\times$ ) of a representative section illustrating the detailed histopathological changes in cFSGS. At this level of magnification, the severe podocyte hyperplasia, segmental capillary collapse, and visceral epithelial cell hyperplasia become more evident. The presence of prominent protein resorption droplets within dilated tubules is also notable, highlighting the severity of glomerular injury in cFSGS. Both micrographs were obtained using Jones silver staining (personal archive of the authors).

Collapsing glomerulopathy is linked to other causes like infections, drugs, and autoimmune diseases. The original description of this variant occurred in the 1980s during the HIV epidemic, but later it was described in other infections such as malaria and visceral leishmaniasis as well [40]. There is some evidence that other viral infections (cytomegalovirus, parvovirus B19, hepatitis C virus, dengue virus, and Zika virus) and systemic immune responses (tuberculosis-induced collapsing glomerulopathy) target podocytes and their proliferative machinery [41–44]. Patients with this variant are usually steroid-resistant and progress to renal failure quickly [2].

#### 2.4.6. C1q Nephropathy

The description of this form of NS was first written by Jennette and Hipp and is still inconclusive [45]. Histological patterns in C1q nephropathy may vary from MCNS to mild mesangial proliferation and to FSGS. Electron microscopy usually shows mesangial electron-dense deposits, especially immunofluorescence staining for C1q. IgG and/or IgM are commonly present as well [46]. These deposits are predominantly located in paramesangial segments, and FP fusion is also reported. Some light microscopic findings of this entity are similar to the findings seen in lupus nephritis, which is an important differential diagnosis of C1q nephropathy. Furthermore, IgA nephropathy and the membranoproliferative pattern of histology may also distinguish the diagnosis via immunofluorescence. However, additional studies are necessary to understand the pathophysiology of C1q nephropathy and improve diagnosis and treatment [46].

### 2.5. Hypotheses Linking Glomerulosclerosis to Podocyte-Derived Alterations

The glomerular development is highly regulated with the podocyte, while its altered biology is a determinant of progression to glomerulosclerosis. Different glomerular diseases have been directly associated with alterations in podocyte functions and biology. Therefore, the central role of these specialized and polarized epithelial cells supports the concept of glomerular diseases as podocytopathies [47]. Although podocyte dysfunction, injury, or loss determine a common factor in the development of NS, many hypotheses propose that the pathogenesis of idiopathic NS is either immune-mediated or due to a genetic variant. The presence of a systemic circulating factor, likely podocyte-derived, has also been suggested [1,6].

#### 2.5.1. Immune-Mediated

The immune system may be involved in the pathogenesis of NS, particularly a dysfunction or dysregulation of T lymphocytes [48]. Some evidence, such as the development of NS after allergic reactions to poisons and stings, reinforces the hypothesis. Furthermore, immunosuppressive agents play a role in NS response and even resolution [1]. In this sense, Lin et al. demonstrated spontaneous NS remission after infection with measles, which triggers prolonged depression of the immune system cells [49]. Chemotherapy for Hodgkin's and other T-cell lymphomas in NS patients also affects the disease outcome. The literature supports an association between NS, especially MCNS, and classical Hodgkin's lymphoma (cHL). MCNS associated with cHL is often dependent on or resistant to steroids, but the remission of NS is linked to the cure of the lymphoma [50]. MCNS can also occur in non-Hodgkin lymphoid disorders [51].

The antigen-presenting cells are responsible for the primary co-stimulatory signal for T-cell activation. CD80 (B7-1) is a protein expressed on those antigen-presenting cells and is the main molecular candidate for the immune-mediated feature in podocytopathies. CD80 binds to CTLA-4, a protein receptor expressed on the T-cell surface, and an increase in podocyte B7-1 expression may cause consequent dysfunction or dysregulation of T lymphocytes [52]. Clinical trials tested CTLA-4 as a therapeutic agent, like abatacept [53] and belatacept [54], in FSGS, but results on efficacy are still conflicting.

#### 2.5.2. Systemic Circulating Factors

A hypothetical cause of NS is the existence of a circulating permeability factor that disturbs the glomerular permeability. It has been suggested that this supposed factor acts on the endothelial cell or podocyte, especially in steroid-resistant NS (SRNS) and FSGS [1]. A study developed in 1996 evaluated in vitro the glomerular permeability to albumin of recurrent FSGS patients. The investigation included the response to treatment and recurrence of FSGS after kidney transplantation in 30 to 40 percent of patients. This study sustains the hypothesis that a circulating factor is related to the recurrence of the disease and to the beginning of renal injury [55]. The existence of a circulating factor was further corroborated by the possibility of maternal transmission of FSGS. However, in utero

exposure did not cause chronic glomerular disease, suggesting that the supposed factor would be smaller than IgG with a molecular weight between 30 and 50 kd and would not remain present in the fetus's circulation [56].

Some molecules have been investigated as potential permeability factors, including hemopexin, heparanase, angiopoietin-like 4 (ANGPTL4), cardiotrophin-like cytokine-1, and suPAR [57–59]. The suPAR is found in the plasma of patients with recurrent FSGS and may lead to FP effacement and posterior proteinuria due to an interaction with  $\alpha 5\beta 3$ -integrin receptors on the surface of podocytes [59]. ANGPTL4 is a glycoprotein expressed in the heart, adipose tissue, and skeletal muscle. Its concentration is elevated in NS. ANGPTL4 has two molecular forms, hyposialylated and sialylated, that trigger different mechanisms to regulate proteinuria [58]. The hyposialylated form is secreted via podocytes and affects GBM and endothelial cells, leading to damage to the filtration barrier and proteinuria [58]. On the other hand, the sialylated form binds to  $\alpha 5\beta 3$ -integrins on the glomerular endothelium and reduces proteinuria. This mechanism has been explored as a potential treatment for NS. However,  $\alpha 5\beta 3$ -integrin activation is lipid-dependent, and it causes hypertriglyceridemia in NS via inhibition of lipoprotein lipase [58].

### 2.5.3. Genetic Variants

Mutations on genes encoding some components of the glomerular barrier, such as the GBM, podocyte, its mitochondria or lysosomes, slit diaphragm, actin cytoskeleton, or its molecular composition, can lead to proteinuria and NS. An understanding of the genes related to NS is important for the management of patients, especially considering the genetic variants and mutations associated with SRNS.

The early identification of genetic causes for SRNS allows for more appropriate management of the disease. Specific mutations in the genes *NPHS1*, *NPHS2*, *LAMB2*, and *WT1* explain 69 to 85% of NS cases starting in the first three months of life. The presence of mutations in these genes decreases to 50 to 66% when NS starts between 4 and 12 months of life. If NS begins after 1 year of age, only 25% of cases are associated with genetic mutations [60]. The early identification of genetic causes supports the discontinuation of immunosuppressive agents and provides more information for prenatal counseling. In addition, the risk of recurrence after kidney transplant is lower in genetic forms of NS than in non-genetic-related syndromes. A multicentric study followed 1340 children with SRNS over 1 year of age and found that 14% of cases were associated with a genetic mutation [61], including polymorphisms of the major histocompatibility complex (HLA). HLA loci mutations represent a genetic risk for SSNS of 4 to 6 percent. However, the association between SSNS and these mutations is found only in specific ethnicities [62,63].

## 3. Molecular and Genetic Markers

### 3.1. Genetic Mutations

In recent years, studies have identified more than 50 genes as causes of NS in different populations. Mutations in the *NPHS1* gene that codes for nephrin, described in 1998, led to an increase in studies searching for mutations in numerous components of the glomerular filtration barrier, including slit diaphragm structure and function, organization of podocyte actin cytoskeleton, biosynthesis of co-enzyme Q, lysosomal pathways, and adhesion to the GBM [33]. To date, the described mutations that caused NS can be divided into different categories, as summarized in Table 2.



**Table 1.** Brief summary of the common histological types of childhood nephrotic syndrome.

Nephrotic Syndrome	Characteristics	Causes	References
Congenital nephrotic syndrome (Finnish type)	Congenital NS is an autosomal-recessive disorder with heavy proteinuria in the neonatal period. A renal biopsy shows many glomeruli with mesangial hypercellularity and hyperlobulated capillary tufts. Proximal and distal tubules may present microcystic dilatation, and the podocytes present FP effacement. It presents nonspecific mesangial IgM, C3, and C1q deposits, detected via immunofluorescence.	The mutated gene related to Finnish nephropathy (FN) is NPHS1, mapped to the long arm of chromosome 19 (19q13.1), which codes for nephrin.	[2]
Diffuse mesangial sclerosis	Electron microscopy shows podocyte hypertrophy and irregular FP effacement. Late stages of DMS exhibit thickened capillary loops, a decrease in capillary lumens, and the formation of a sclerotic mass in the mesangium.	WT1 gene mutations in exons 8 or 9 are possible causes.	[2,18]
Focal segmental glomerular sclerosis Cellular FSGS	FSGS is related to the presence of segmental sclerotic lesions within the glomeruli. It presents hypercellularity and endocapillary proliferation with luminal obliteration of capillaries.	Some molecules: cardiotrophin-like cytokine factor 1, apoA1b (an isoform of ApoA1), anti-CD40 antibody, and serum urine-type plasminogen activator receptor (suPAR). More than 50 genes are potential factors for monogenic forms of FSGS. Drugs and anabolic steroid abuse are other factors.	[2,6,24–27,29–32]
Primary FSGS with mesangial hypercellularity Familial FSGS	This type is associated with mesangial hypercellularity in the non-sclerotic glomeruli. It exhibits loss of podocin staining, detected using immunohistochemistry methods.	Mutations in the NPHS2 gene, which codes for podocin.	[2,18]
Secondary FSGS	This type presents mesangial hypercellularity, mesangial IgA, and basement membrane abnormalities.	IgA nephropathy, hereditary nephritis (Alport's syndrome), and lupus nephritis.	[2,51–53]
Collapsing glomerulopathy	It is related to the implosive collapse of the capillary loops with alterations of the basement membrane and hypertrophy and hyperplasia of podocytes.	COQ2 mutations that cause mitochondrial disorders. HIV, malaria, visceral leishmaniasis, cytomegalovirus, parvovirus B19, hepatitis C virus, dengue virus, and Zika virus are possible factors.	[2,55–59]

NS: Nephrotic Syndrome; DMS: Diffuse Mesangial Sclerosis; FSGS: Focal Segmental Glomerulosclerosis; FP: Foot Process; GBM: Glomerular Basement Membrane; WT1: Wilms Tumor 1 Gene; NPHS1: Nephrin Gene; NPHS2: Podocin Gene; COQ2: Coenzyme Q2 Gene; suPAR: Soluble Urokinase-type Plasminogen Activator Receptor; HIV: Human Immunodeficiency Virus; Alport's syndrome: Hereditary Nephritis; and IgA: Immunoglobulin A.

**Table 2.** Summary of genes related to the development of childhood nephrotic syndrome.

Gene	Function/Description	Mutations and Associated Conditions	Chromosome Location	Mode of Inheritance	References
Slit-diaphragm-associated mutations					
CD2AP	Acts as a bridge between the SD and the actin cytoskeleton. Lack of expression causes mesangial cell proliferation, glomerulosclerosis, and NS.	Mutations alter the SD structure. CD2AP <sup>-/-</sup> mice develop severe NS.	6p12.3	Autosomal Recessive and Dominant	[64–66]
NPHS1	Encodes nephrin. Mutations account for 40–60% of infants with congenital NS. Malfunction leads to massive protein loss.	Mutations associated with Finnish-type nephrotic syndrome.	19q13.12	Autosomal Recessive	[67–69]
NPHS2	Encodes podocin. Plays a role in recruiting nephrin to the SD. Mutations lead to congenital/infantile NS and SRNS.	Mutations lead to childhood- or adult-onset SRNS.	1q25.2	Autosomal Recessive	[70,71]
CRB2	Encodes the Crumbs cell polarity complex protein	Mutations lead to SRNS with FSGS.	9q33.3	Autosomal Recessive	[72–74]
FAT1	Encodes the tumor suppressor of the cadherin superfamily.	Mutations lead to a combination of SRNS, tubular ectasia, hematuria, and neurological involvement.	4q35.2	Autosomal Recessive	[75–78]

Table 2. Cont.

Gene	Function/Description	Mutations and Associated Conditions	Chromosome Location	Mode of Inheritance	References
<i>PLCE1</i>	Encodes the Phospholipase C epsilon 1 (PLC $\epsilon$ 1) protein.	Mutations in <i>PLCE1</i> are responsible for a major part of cases of Mesangial Sclerosis.	10q23.33	Autosomal Recessive	[79,80]
<i>TRPC6</i>	Encodes the Transient Receptor Potential Cation Channel Subfamily C member 6 receptor.	Mutations lead to late-onset FSGS.	11q22.1	Autosomal Dominant	[81–84]
Actin-cytoskeleton-associated mutations					
<i>ACTN4</i>	Encodes alpha-actin 4, an actin-binding protein in the FPs of podocytes.	Mutations associated with adult-onset SRNS with FSGS.	19q13.2	Autosomal Recessive	[85–87]
<i>ANLN</i>	Encodes anilin, an actin-binding protein. Mutations cause a reduction in CD2AP binding, dysregulating signaling in podocytes.	Mutations lead to disarrangement in the SD.	7p14.2	Autosomal Dominant	[88,89]
<i>ARHGAP24</i>	Encodes the Rho GTPase-activating protein 24.	Mutations associated with familial SRNS in the second and third decades of life.	4q21.3	Autosomal Dominant	[90,91]
<i>ARHGDI1</i>	Encodes the RhoGDP dissociation inhibitor $\alpha$ .	Mutations associated with congenital NS or SRNS within the first 2 years.	17q25.3	Autosomal Recessive	[92,93]
<i>INF2</i>	Encodes inverted formin 2 and regulates actin polymerization. Mutations related to Charcot–Marie–Tooth disease and FSGS.	Mutations related to Charcot–Marie–Tooth disease and FSGS.	14q32.33	Autosomal Dominant	[94,95]
<i>MYO1E</i>	Encodes non-muscular myosin 1E, an actin-binding molecular motor in the FPs of podocytes.	Mutations lead to SRNS with focal thickening, disorganization, and multilamination of GBM.	15q22.2	Autosomal Recessive	[96–98]
<i>KANK1</i>	Encodes kidney ankyrin repeat-containing protein 1.	Mutations cause congenital and early childhood onset NS.	9p24.3	Autosomal Recessive	[99,100]
<i>KANK2</i>	Encodes kidney ankyrin repeat-containing protein 2.	Mutations cause congenital and early childhood onset NS.	19p13.2	Autosomal Recessive	[99,101]
<i>KANK4</i>	Encodes kidney ankyrin repeat-containing protein 4.	Mutations cause congenital and early childhood onset NS.	1p31.3	Autosomal Recessive	[99,102]
Mitochondrial protein mutations					
<i>ADCK4</i>	Has a role in the synthesis of Coenzyme Q10 (CoQ10), a lipid-soluble ubiquinone.	Mutations cause SRNS.	19q13.1	Autosomal Recessive	[103–105]
<i>COQ2</i>	Encodes parahydroxybenzoate-polyprenyltransferase, involved in the biosynthesis of ubiquinone CoQ10.	Mutations lead to CoQ10 deficiency, resulting in SRNS.	4q21.23	Autosomal Recessive	[106,107]
<i>COQ6</i>	The product is a mono-oxygenase required for CoQ10 biosynthesis. Mutations lead to primary CoQ10 deficiency.	Mutations result in primary CoQ10 deficiency, leading to SRNS.	14q24.3	Autosomal Recessive	[108–111]
<i>PDSS2</i>	Encodes decaprenyl diphosphate synthase, subunit 2, a component of a heterotetrameric decaprenyl synthase.	Mutations lead to primary CoQ10 deficiency, resulting in SRNS.	6q21	Autosomal Recessive	[112–114]
Glomerular-basement-membrane-related mutations					
<i>COL4A3</i>	Encodes Collagen Type IV alpha-3 chain.	Mutations related to Alport syndrome type 2 and autosomal dominant or recessive modes of inheritance for benign familial hematuria.	2q36.3	Autosomal Dominant (Alport syndrome type 3), Autosomal Recessive (Alport syndrome type 2)	[115–119]
<i>COL4A4</i>	Encodes Collagen Type IV alpha-4 chain.	Mutations related to Alport syndrome type 2 and autosomal dominant or recessive modes of inheritance for benign familial hematuria.	2q36.3	Autosomal Dominant (Alport syndrome type 3), Autosomal Recessive (Alport syndrome type 2)	[115–119]

Table 2. Cont.

Gene	Function/Description	Mutations and Associated Conditions	Chromosome Location	Mode of Inheritance	References
<i>COL4A5</i>	Encodes Collagen Type IV alpha-5 chain.	Mutations related to Alport syndrome type 1, exhibiting X-linked dominant mode of inheritance.	Xq22	X-Linked Dominant	[115,116,118–120]
<i>ITGA3</i>	Encodes integrin alpha-3 chain and forms an integrin-family molecule, VLA-3.	Mutations associated with interstitial lung disease, NS, and congenital epidermolysis bullosa.	17q21.33	Autosomal Recessive	[121–123]
<i>ITGB4</i>	Encodes integrin beta-4 chain and forms the alpha-6-beta-4 integrin molecule.	Mutations associated with congenital FSGS and epidermolysis bullosa with pyloric atresia.	17q25.1	Autosomal Recessive	[124–126]
<i>LAMB2</i>	Encodes laminin beta-2 chain. Mutations associated with Pierson syndrome.	Mutations cause Pierson syndrome, presenting as congenital NS with mesangial sclerosis and eye abnormalities.	3p21	Autosomal Recessive	[127,128]
Nuclear transcription factors and protein mutations					
<i>LMX1B</i>	Encodes LIM homeobox transcription factor.	Mutations cause FSGS and nail–patella syndrome.	9q32-34.1	Autosomal Dominant	[129–131]
<i>NXF5</i>	Belongs to a multigene family of nuclear RNA export factors. Role in FSGS is not well understood.	Mutations might contribute to FSGS, but their significance is unknown.	X chromosome	X-Linked Recessive	[132,133]
<i>SMARCAL1</i>	Encodes SWI/SNF-related matrix-associated, actin-dependent regulator of chromatin.	Mutations result in Schimke immunosseous dysplasia and NS.	2q34.36	Autosomal Recessive	[134–136]
<i>WT1</i>	Encodes a zinc finger DNA-binding protein. Mutations associated with Wilms Tumor, Denys–Drash Syndrome with NS, somatic mesothelioma, and other diseases.	Mutations associated with Wilms Tumor, Denys–Drash Syndrome with NS, somatic mesothelioma, and other diseases.	11p13	Autosomal Dominant (Wilms Tumor, Denys–Drash Syndrome), Somatic Mutation	[137–142]
<i>OSGEP</i>	Encodes O-sialoglycoprotein endopeptidase. Mutations lead to Galloway–Mowat syndrome and GBM disorder.	Mutations cause Galloway–Mowat syndrome and GBM disorder.	14q11.2-12	Autosomal Recessive	[143–145]
<i>LAGE3</i>	Encodes L-antigen family member 3.	Mutations cause X-linked Galloway–Mowat syndrome with NS and primary microcephaly.	Xq28	X-Linked Recessive	[146,147]
<i>WDR73</i>	Encodes WD repeat-containing protein 73.	Mutations cause Galloway–Mowat syndrome with microcephaly and SRNS.	15q25.2	Autosomal Recessive	[148–150]
<i>TP53RK</i>	Encodes p-53-related protein kinase.	Mutations cause Galloway–Mowat syndrome.	20q13.2	Autosomal Recessive	[146,151]
<i>NUP93</i>	Encodes nucleoporin 93 kd, a subunit of the 12 million Da nuclear pore complex.	Mutations cause SRNS.	16q13	Autosomal Recessive	[152,153]
<i>NUP107</i>	Encodes nucleoporin 107 kd, a subunit of the 120 million Da nuclear pore complex.	Mutations cause SRNS and ovarian dysgenesis.	12q15	Autosomal Recessive	[154–156]
<i>NUP205</i>	Encodes nucleoporin 205 kd, a subunit of the 120 million Da nuclear pore complex.	Mutations cause SRNS.	7q33	Autosomal Recessive	[153,157]
<i>XPO5</i>	Encodes exportin 5.	Mutations associated with early onset NS.	6p21.1	Autosomal Recessive	[153,158]

Table 2. Cont.

Gene	Function/Description	Mutations and Associated Conditions	Chromosome Location	Mode of Inheritance	References
Proximal tubule protein reabsorption mutations					
<i>CUBN</i>	Encodes cubilin, the intestinal receptor for endocytosis of intrinsic factor, vitamin B12, and a receptor in epithelial apoA-I/HDL metabolism.	Mutations cause Imerslund–Grasbeck syndrome, low molecular weight proteinuria, and megaloblastic anemia.	10p13	Autosomal Recessive	[159,160]
<i>AMN</i>	Encodes amnion-associated transmembrane protein. Along with cubilin, it forms a receptor complex called “cubam.”	Mutations cause Imerslund–Grasbeck syndrome with B12 deficiency and proteinuria.	14q32	Autosomal Recessive	[161–163]
<i>LRP2</i>	Encodes low-density lipoprotein receptor-related protein 2 or megalin.	Mutations cause Donnai–Barrow syndrome with facial anomalies, ocular alterations, sensorineural hearing loss, and NS.	2q31.1	Autosomal Recessive	[164–166]
Other mutations					
<i>CFH</i>	Encodes complement factor H, a serum glycoprotein that regulates the function of the alternative complement pathway.	Mutations associated with atypical hemolytic uremic syndrome and C3 glomerulopathy.	1q31.3	Autosomal Dominant	[167–170]
<i>DGKE</i>	Encodes diacylglycerol kinase epsilon, an intracellular molecule that phosphorylates diacylglycerol (DAG) to phosphatidic acid.	Mutations associated with susceptibility to atypical hemolytic uremic syndrome and NS.	17q22	Autosomal Recessive	[171,172]
<i>PMM2</i>	Encodes phosphomannomutase, an enzyme necessary for the synthesis of GDP-mannose.	Mutations cause congenital disorders of glycosylation type I and SRNS.	16p13.2	Autosomal Recessive	[173–175]
<i>PTPRO</i>	Encodes protein-tyrosine phosphatase receptor-type O or glomerular epithelial protein 1.	Mutations cause childhood-onset NS with varying severities.	12p12.3	Autosomal Recessive	[176,177]
<i>SCARB2</i>	Encodes scavenger receptor class B, member 2, a lysosomal integral membrane glycoprotein.	Mutations cause progressive myoclonic epilepsy, with or without renal failure and SRNS.	4q21.1	Autosomal Recessive	[178–181]
<i>ZMPSTE24</i>	Encodes zinc metalloproteinase STE24, a protein involved in the metabolism of farnesylated proteins.	Mutations cause mandibuloacral dysplasia type B, increasing the risk for FSGS.	1p34.2	Autosomal Recessive	[182,183]
<i>ALG1</i>	Encodes chitobiosylidiphosphodolichol beta-mannosyltransferase, a protein that acts in the glycosylation process.	Mutations cause congenital disorder of glycosylation type Ik, producing congenital NS.	16p13.3	Autosomal Recessive	[184–186]
<i>EMP2</i>	Encodes epithelial membrane protein 2, which regulates cell membrane composition and plays a role in glomerular filtration.	Mutations cause childhood-onset NS.	16p13.2	Autosomal Recessive	[187–189]
<i>TTC21B</i>	Encodes tetratricopeptide repeat domain-containing protein 21B, involved in ciliary function.	Mutations cause nephronophthisis, FSGS, and short-rib thoracic dysplasia.	2q24.3	Autosomal Recessive	[190–193]
<i>SGPL1</i>	Encodes sphingosine-1-phosphate lyase 1, involved in sphingolipid catabolism.	Mutations cause primary adrenal insufficiency and SRNS.	10q22.1	Autosomal Recessive	[194,195]



### 3.2. Molecular Markers

The clinical characteristics of NS are commonly not predictive of patient outcomes [196]. The response to steroids has been associated with better outcomes in NS [197]. For patients with SRNS, renal biopsy is recommended to evaluate the prognosis and histopathological subtype, but it is an invasive procedure not free of complications, especially in children [198]. Furthermore, the incorrect interpretation and inadequate preparation of kidney tissue may lead to the wrong evaluation. Nevertheless, it is considered a generally safe procedure, especially when performed by trained nephrologists [199]. Therefore, new and less invasive biomarkers are necessary to predict disease outcomes, mainly for the pediatric age group. Indeed, urine is considered the ideal sample to search for biomarkers in renal diseases [200], but biomarkers in serum or plasma samples have also been evaluated in patients with NS.

#### 3.2.1. MicroRNAs

Current studies have shown that microRNAs are a potential non-invasive biomarker that can help in the diagnosis of NS [200,201]. Some microRNAs, including hsa-miR-181a, hsa-miR-210, hsa-miR-30a, hsa-miR-942, hsa-miR-192, and hsa-miR-586, are up-regulated and detected in the serum of patients with NS. These markers might be associated with clinical findings in NS [201]. Another study showed that exosomal microRNAs, including miR-194-5p, miR-146b-5p, miR-378a-3p, miR-23b-3p, and miR-30a-5p, were found in the urine of patients with NS and might serve as novel biomarkers for diagnosing, monitoring, and stratifying pediatric patients with NS [200].

More recently, Bayomy et al. [202] showed in a cohort of children with NS that the measurement of miR-142a-5p in blood samples was capable of predicting SRNS with high accuracy (AUC = 0.965), suggesting the possible role of autoimmunity in the pathogenesis of NS and the resistance to steroids. Similarly, Zhang et al. [203] reported that miR-17-5p was significantly more expressed in the peripheral blood of pediatric patients with NS when compared to healthy controls. Nevertheless, most studies explored microRNAs in only one ethnicity, making multicenter studies necessary.

#### 3.2.2. Proteomics

The study of urinary proteomics holds promise for identifying and predicting markers of renal disease in children [204]. Additionally, urinary proteomics is more stable than the blood proteome and closely matches pathological changes in the kidney and urogenital tract [205]. Some proteins that can be reliable biomarkers are only found in the urine. The pathogenesis of NS is strongly associated with alterations in the glomerular barrier and an increase in permeability to albumin. Additionally, a number of renal membrane proteins and receptors are subject to regulation via glycosylation [206].

Alfa 1-B glycoprotein (A1BG) is part of the immunoglobulin superfamily, but its function is still unclear. Piyaphanee et al. [207] used a proteomics approach to evaluate the urine of patients with idiopathic NS and healthy controls. A fragment of A1BG was exclusively identified in patients diagnosed with NS. A 13.8 kd fragment was only seen in patients with SRNS but not in patients with SSNS [207]. Nonetheless, no further studies were performed to validate these results, though A1BG seems to be a promising biomarker. In a similar approach, Bennett et al. [208] used a proteomics panel of 10 biomarkers (including A1BG) in the urine of 50 children with idiopathic NS. This panel showed a high capacity for predicting steroid responsiveness (AUC of 0.92). Nonetheless, multicenter studies are needed to validate the results found with this proteomics panel.

#### 3.2.3. Inflammatory Markers, Cytokines, and Chemokines

One of the most commonly evaluated markers is inflammatory molecules. To date, urinary and blood levels of cytokines and chemokines often differ in NS patients if compared to healthy controls. Some studies have provided evidence that upregulation of interleukin (IL)-2 and its soluble receptor (sIL2R) may be involved not only in the pathophysiology of NS but also in steroid resistance to treatment by increasing the *MDR1* gene expression

of its product, P-glycoprotein [209]. Another biomarker that can help in the detection of steroid-resistant patients is suPAR. Even though this marker cannot distinguish the histopathological type of NS, it can be helpful in predicting steroid resistance in children with primary NS [210].

Chemokines, an extensive category of low-molecular-weight cytokines, predominantly function in the recruitment of leukocyte subsets during both homeostatic conditions and inflammation. These molecules hold promise as molecular markers owing to their pivotal roles in the pathophysiology of pediatric renal diseases [211]. The assessment of these inflammatory mediators presents potential utility in managing diverse renal conditions in children and identifying individuals at heightened risk for chronic kidney disease (CKD). The prevailing evidence underscores that the infiltration of leukocytes, orchestrated via inflammatory chemokines emanating from various cellular sources, has the potential to augment inflammatory responses within the kidney [212].

Multiple methodologies are available for quantifying chemokine levels, encompassing both protein and mRNA, in tissues and body fluids. Direct measurement of chemokines in renal tissue can be accomplished through immunohistochemical or immunofluorescent techniques, or their concentrations can be gauged in the supernatants of homogenized tissues. Conversely, less invasive approaches, such as enzyme-linked immunosorbent assays (ELISA) or flow cytometry-based techniques employing plasma and serum, prove to be more clinically useful for assessing chemokine levels in urine or blood samples [211].

The measurement of specific cytokines and chemokines emerges as a valuable tool in discerning between histopathological types of NS. Notably, patients with MCNS exhibit compromised T regulatory cells, accompanied by diminished levels of IL-10 [213]. Furthermore, distinctions between FSGS and MCNS may be drawn through urinary levels of the fibrogenic cytokine transforming growth factor beta (TGF- $\beta$ ), although its applicability as a biomarker for steroid responsiveness remains inconclusive [214]. Significantly elevated urinary levels of the chemokine monocyte chemoattractant protein 1 (MCP-1/CCL2) were observed in FSGS patients relative to counterparts with uropathies at equivalent CKD stages [71]. Additionally, urinary MCP-1/CCL2 levels exhibited positive correlations with serum total cholesterol and triglyceride concentrations [215]. These concentrations demonstrated noteworthy positive associations with occult blood in urine and inverse relationships with the estimated glomerular filtration rate. Moreover, urinary MCP-1/CCL2 concentrations displayed substantial correlations with histological chronicity indices in patients diagnosed with lupus nephritis and IgA nephropathy [216]. This supports the contention that the assessment of this chemokine holds promise as a noninvasive method for predicting the activity of glomerular diseases in the pediatric population.

Cardiotrophin-like cytokine factor 1 (CLCF-1) is a cytokine present in the IL-6 family. Savin et al. showed that a single intraperitoneal injection of CLCF-1 in C57Bl6 mice increased the urine albumin/creatinine ratio, and the chronic infusion of the cytokine induced segmental sclerosis in rare glomeruli [24]. These findings suggest that CLCF-1 might be involved with the development of FSGS in humans. Nonetheless, in patients with FSGS and MCNS, serum levels of CLCF-1 were not associated with renal function nor with histological markers of kidney injury [217]. Therefore, its role as a biomarker for NS is still unclear.

#### 3.2.4. Other Potential Markers

Proteins found in the urine of NS patients named R6703, R7210, R11820, and R14356 are differentially expressed in SRNS and can be used to suggest treatment for NS patients [218]. Similarly, lower levels of APOL1 in urine are suggestive of SRNS. Other urinary biomarkers of NS, which were specifically associated with FSGS, included alpha 2 macroglobulin, retinol binding protein 4, and orosomucoid 2. Alpha 2 macroglobulin had the highest predictive power for the diagnosis of FSGS [219].

The vitamin D-binding protein (VDB) and APOL1 were regarded as candidate predictive biomarkers for steroid-resistant nephrotic syndrome (SRNS). Similarly, hemopexin

(HPX), adiponectin (ADIPOQ), and sex hormone-binding globulin (SHBG) have been proposed as candidate biomarkers for mechanistically differentiating SRNS from SSNS [220]. VDB deserves special attention since vitamin D may play an essential role in the pathophysiology of NS. Patients with NS have high levels of vitamin D in their urine but low serum levels [221,222]. Urinary VDB levels were significantly higher in patients with SRNS in comparison to those with SSNS [223].

Neutrophil gelatinase-associated lipocalin (NGAL) is expressed at low levels in the kidney [224] and is considered an initial marker of renal injury [225]. In addition, NGAL has been considered a notable predictor of disease evolution in patients with chronic kidney disease [226,227]. In that sense, Bennet et al. [228] compared urinary NGAL levels between patients with SSNS, SRNS, and healthy controls. Not only did the authors find that urine NGAL levels were clearly higher in patients with SRNS when compared to the other two groups, but urinary NGAL was a good biomarker for predicting steroid-responsiveness (AUC of 0.91) [228]. As a result, NGAL levels may be a good predictor for steroid resistance in patients with NS. Nevertheless, it is relevant to consider that these results need to be validated in a larger cohort of patients.

### 3.3. Metabolomics

Metabolomics comprises a robust set of tools for phenotype analysis, hypothesis generation, and subsequent testing. The execution of metabolomics involves employing analytical technologies capable of generating diagnostic patterns through fingerprinting and achieving absolute quantitation of specific targeted metabolites [229]. Metabolomics has become an invaluable analytical tool for discerning urinary and serum biomarkers associated with renal diseases [230]. The thorough exploration of the metabolome stands as a pivotal method for investigating the phenotype and its alterations induced by environmental factors, pathological conditions, or variations in genotype.

Studies employing a combined proteomics and metabolomics approach, utilizing label-free mass spectrometry, have unveiled, for the first time, the implication of the glycoprotein afamin and several specific metabolites—hydroxyphenylacetate, uridine, glutamate, and phenylalanine—in the pathogenesis of primary NS [231]. Importantly, analogous patterns were evident in both protein and metabolite datasets, underscoring the potential of this integrated approach for advancing non-invasive diagnostic strategies for NS and its possible incorporation into routine clinical screening procedures for the condition.

Using a metabolomic discovery approach [232], Gooding et al. found a small group of candidate biomarkers predictive of SRNS in pediatric patients, such as glutamine and malonate. Through paired-sample analyses, a broader set of potential candidate metabolite biomarkers has been identified, offering insights into specific mechanistic molecular pathways and targets associated with steroid resistance. This expanded group includes lipoproteins, adipate, pyruvate, creatine, glucose, tyrosine, valine, and glutamine [232]. Additionally, glucocorticoid treatment in children with SRNS has been found to induce changes in a singular endogenous metabolite, sn-glycero-3-phosphocholine, distinguishing it from individuals with SSNS. Collectively, these findings pinpoint specific candidate metabolite biomarkers capable of predicting SRNS at the onset of the disease, while also highlighting potential therapeutic target pathways that could pave the way for the future development of more precise and effective treatments for NS.

### 3.4. Biomarkers Associated with Histological Features

The morphological picture of glomerulopathies is of great practical importance since, among all kidney diseases, they are the most diagnosable with a renal biopsy. The same form of clinical presentation can relate to very different morphological lesions with different pathogenic mechanisms, prognosis, and therapeutic approaches. Similarly, a morphological lesion pattern can be associated with different etiologies, involving specific prognosis and treatment.

Although kidney biopsy is the gold standard for NS diagnosis, this kind of invasive procedure is not routinely performed in children [233]. It is usually requested in certain specific situations, such as when there is the possibility of a coexisting nephritic syndrome or when the patient is evolving with symptoms that are not typically associated with MCNS, such as hypertension, altered renal function, gross hematuria, hypocomplementemia, and steroid resistance [234].

Generally, patients with FSGS present a low percentage (20%) of remission with steroid therapy. Thus, these patients are more likely to be submitted for a renal biopsy. On the other hand, about 90% of patients with MCNS are steroid-sensitive, and, for this reason, renal biopsies are not indicated [11]. With the purpose of minimizing the number of unnecessary biopsies, especially in children, there are some biomarkers associated with histological features that can help establish whether this procedure is really needed.

#### 3.4.1. Transforming Growth Factor Beta (TGF- $\beta$ )

It is known that TGF- $\beta$  is overexpressed by podocytes in patients who are diagnosed with progressive podocytopathies, especially FSGS. This cytokine regulates the hypertrophy, proliferation, and apoptosis of renal cells. TGF- $\beta$  also stimulates extracellular matrix (ECM) protein synthesis, GBM thickening, and mesangial matrix expansion [235]. Considering these actions, TGF- $\beta$  could serve as a potential diagnostic biomarker in NS. In addition, this cytokine is correlated with hypoalbuminemia and dyslipidemia, which are typical clinical features of NS [236].

#### 3.4.2. CD44

Another molecule that can play an important role as a histopathological marker is CD44. The expression of this glycoprotein, which is considered a marker of activated podocytes and parietal epithelial cells (PECs), has been implicated in the progression of renal fibrosis and the pathogenesis of FSGS. Therefore, CD44 immunostaining in PECs allows the differentiation of FSGS from MCNS. Patients with significantly increased PEC-CD44-positive renal tissue exhibited faster deterioration of renal function and the characteristics of typical FSGS [237,238].

#### 3.4.3. CD80

CD80 (B7-1) is a co-stimulatory molecule that has been reported to be expressed in patients who have been diagnosed with glomerular diseases [239], especially those with FSGS. Expressed on antigen-presenting cells, this histological marker significantly contributes to T-cell activation. CD80, a key player in this process, is modulated via the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), primarily found on regulatory T cells (Tregs) [240]. Therefore, the detection of CD80 in the renal tissue of patients with SRNS indicates lower amounts of Tregs [241].

#### 3.4.4. Extracellular Vesicles

Extracellular vesicles (EVs) are small, membrane-enclosed structures released via cells into the extracellular environment that play a crucial role in intercellular communication by carrying and transferring various bioactive molecules, including proteins, lipids, and nucleic acids (such as RNA and DNA), between cells. EVs have been implicated in various physiological and pathological processes, including immune response regulation, tissue repair, and the progression of diseases. In that sense, Eroglu et al. (2021) have found that patients with SSNS during relapse had higher protein content in circulating plasma EVs, especially proteins that involved actin cytoskeleton rearrangement, such as Ras-related C3 botulinum toxin substrate 1 (RAC-1) [242]. EVs have also been shown to induce mesangial cell proliferation in pediatric patients with FSGS through the phospho-STAT-3 pathway [243]. This topic has been recently reviewed elsewhere [244].



#### 4. Conclusions

NS is a very complex disease with different outcomes, therapeutic responses, and histopathological patterns. The most characteristic finding of NS is the presence of podocytopathy. The function and/or the structure of the components of the podocytes can be altered through several mechanisms, including gene mutations, immunologic alterations, infectious diseases, and circulating factors. The pathophysiology of NS is still not fully understood.

There are potential biomarkers that can help with understanding the pathophysiology of NS. The advances in this research field might improve the clinical outcomes and therapeutic approaches of patients with NS. Furthermore, recent studies showing that different methods of assessing urinary molecules are less invasive and potentially more accurate for diagnosing SRNS are of particular importance for pediatric patients.

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