Chapter 7
Focal Segmental Glomerulosclerosis and Its Pathophysiology

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Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
APOL1	Apolipoprotein L1
ARB	Angiotensin receptor blocker
BP	Blood pressure
CLC-1	Cardiotrophin-like cytokine 1
CNI	Calcineurin inhibitor
COQ	Coenzyme Q
ESRD	End stage renal disease
FSGS	Focal segmental glomerulosclerosis
HAN	Heroin associated nephropathy
HIVAN	Human immunodeficiency virus associated nephropathy
KDIGO	Kidney disease improving global outcomes
MAP	Mean arterial pressure
MMF	Mycophenolate mofetil
mTOR	Mechanistic target of rapamycin
RAAS	Renin angiotensin aldosterone system
suPAR	Soluble urokinase plasminogen activator receptor
TGF-β	Transformimg growth factor beta
TNFα	Tumor necrosis factor alpha
TRPC6	Transient receptor potential cation channel 6

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7.1 Introduction

Focal segmental glomerulosclerosis (FSGS) is a morphological finding on light microscopy of renal tissue that has become synonymous with a progressive proteinuric kidney disease. As the name may suggest, FSGS is when some (or focal) glomeruli have sclerosis (or scarring) in segments of the glomerular tuft. This pattern is typically seen early in the disease process but can become more extensive as the disease evolves [1, 2]. This pattern of scarring is not unique to a singular cause and is applied to kidney diseases caused by genetic mutations, viral infections, medications, toxins, reduced renal mass, or a "permeability factor". Though the causes of this disease may be quite diverse, injury afflicted on the podocyte is what leads to scarring of the glomerulus and proteinuria [1].

7.2 Primary FSGS

Typically when the term "primary" is applied to other disease states, such as primary immune deficiency, it refers to an in-born deficiency or mutation. Conversely, "Primary FSGS" is usually only applied to the idiopathic form of the disease. In fact, leading experts in the area of FSGS typically classify genetic causes as a secondary form of FSGS [1–3]. Given the difference between FSGS and other disease classification standards, it can create confusion and debate among those not familiar with the terminology by which FSGS is classified.

Idiopathic FSGS, as the name suggests, is caused by an entity not fully understood at present. It has been suggested that idiopathic FSGS shares some commonality with minimal change disease. Proponents of such an association cite the fact that early histologic changes in idiopathic FSGS are similar to minimal change disease. There are documented cases of patients presenting with nephrotic syndrome and initial biopsies which reveal minimal change disease histology with subsequent biopsies revealing progression to FSGS [1]. Challengers to this theory suggest these observations maybe a result of sampling error given that the changes of FSGS, by definition, only affect some glomeruli and could easily be missed given the limited amount of tissue obtained on a normal biopsy. Either way, FSGS and minimal change disease are similar in that both result in a proteinuric renal disease and are primarily diseases of podocytes. In addition, the causes of both minimal change disease and FSGS are not fully understood.

Several observations about idiopathic FSGS have generated a possible theory for its cause [4]. First, proteinuria and recurrent disease can develop within minutes after transplantation in recipients with idiopathic FSGS [5–7]. Second, when serum from idiopathic FSGS patients was injected into rats, the previously healthy rats developed proteinuria [8, 9]. Third, there are reports of pregnant women with idiopathic FSGS who delivered children that had transient proteinuria immediately after birth [10]. Fourth, there is improvement in the amount of proteinuria in patients with recurrent FSGS who were treated with plasma exchange or protein absorption

[11, 12]. Finally, when kidneys with recurrent FSGS are re-transplanted into patients with kidney disease other than FSGS, the proteinuria and histological changes resolve [13, 14]. These observations suggest the cause of the disease is intrinsic to the individuals' blood and not the kidney itself. Therefore, it has been theorized that the disease is caused by a circulating permeability factor that attacks and damages the podocytes. The exact identity of this permeability factor has yet to be delineated, although a few proteins have been identified as potential sources.

Cardiotrophin-like cytokine 1 (CLC-1), is part of the IL-6 family and is believed to be produced by CD34+ stem cells and is inactivated by galactose *in vitro* [1, 15]. It has been observed that patients with idiopathic FSGS have an overabundance of CLC-1 in their sera when compared to those without the disease [16]. Podocytes have a receptor for CLC-1 that is noted to be upregulated in patient with recurrent FSGS and in patients with idiopathic FSGS when there is an overabundance of this cytokine in the sera [17]. McCarthy et al. also report that CLC-1 can induce proteinuria in experimental models and decrease podocyte expression of nephrin, an important protein that is needed for maintenance of the slit diaphragm. Additionally, anti-CLC-1 antibody when used with both isolated rat glomeruli and FSGS patients' sera has been shown to mitigate the permeability of albumin through the glomeruli [16]. However, the role of CLC-1 *in vivo* is not as well demonstrated. Additionally, the use of galactose infusions, which should inactivate CLC-1, has failed to consistently prevent recurrent FSGS clinically [3].

Another proposed factor is soluble urokinase plasminogen activator receptor (suPAR). Urokinase plasminogen receptor (uPAR) is a receptor that can be found on podocytes and is involved with cell migration and slit diaphragm maintenance by forming signaling complexes with cell membrane proteins such as αvβ3 integrin [18]. The soluble form, suPAR, can be released from the plasma membrane by leukocytes and podocytes, and has been demonstrated to be increased in FSGS [19]. When suPAR undergoes cleavage and glycosylation, it is believed to make an isoform that would fit the characteristic of the theorized causative factor for FSGS [4]. It has been reported that suPAR levels are higher in patients with FSGS compared to other diseases with similar proteinuria and, in cohort studies, the majority of FSGS patients have elevated suPAR levels in the serum [1, 19]. SuPAR has also been noted to be elevated in patient with recurrent FSGS after transplantation [20]. Additionally, in one study, when mice were given injections of suPAR they developed glomerular deposits of suPAR that were associated with podocyte effacement, proteinuria, renal dysfunction, and glomerular damage [4, 18, 19]. Finally, observation studies have suggested that patients treated with plasmapheresis that resulted in lower suPAR levels were associated with reduced proteinuria and remission [4]. However, it has been noted that there was no significant difference in suPAR levels between FSGS and non-FSGS patients when matched for estimated renal function [21] and that suPAR can be elevated in FSGS caused by genetic mutations [22]. Furthermore, pre-transplant serum suPAR levels did not correlate with recurrent disease [23]. Moreover, Cathelin et al. demonstrated that suPAR glomerular deposits do not necessarily result in proteinuria and abnormal podocyte features [24]. For these reasons, some have proposed elevated suPAR levels may be more of a correlation, rather than a causative agent, in primary FSGS but more studies are needed.

7.3 Secondary FSGS

As mentioned above, FSGS histology represents a common end result for a multitude of causes. Secondary causes include etiologies such as genetic disorders, viral infections, drug related, or the result of an adaptive change.

7.3.1 Genetics

In recent years, several genetic mutations have been determined to be associated with renal dysfunction and histologic morphology of FSGS (see Table 7.1). Each of the mutations result in abnormalities in one of six broad categories: (1) slit-diaphragm related molecules, (2) podocyte actin cytoskeleton, (3) podocyte signaling, (4) podocyte gene transcription, (5) molecules for adhesion or extracellular matrix, or (6) mitochondrial DNA or COQ synthesis (Table 7.1 [3, 25–29]). Although these mutation share commonality in their renal manifestations, these mutations also occur in other organ systems and can be associated with a wide array of other clinical manifestations.

A particular area of interest recently is the association with FSGS, hypertensive nephrosclerosis, and HIV-associated nephropathy in African descendants and the roles that apolipoprotein L1 (APOL1) and myosin heavy chain 9 (MYH9) play in these diseases. Kao et al. and Kopp et al. noted in 2008 an association between variants in myosin heavy chain 9 (*MYH9*) gene on chromosome 22 and FSGS in African Americans [30, 31]. However, a causative variant for the *MYH9* associated FSGS could not be identified. With additional research a variant in the neighboring *APOL1* gene was identified and determined to have a much stronger association with the disease [32, 33]. *APOL1* is a gene encoding for apolipoprotein L1 (also called APOL1), a lipoprotein that is part of a larger APOL family involved in innate immunity [34]. The *APOL1* gene has 2 variant alleles, G1 and G2, which represent a missense and a deletion mutation, respectively, compared to the non-pathological allele, G0. The G1 and G2 variants are recessive and individuals have an increased likelihood of developing kidney disease if two risk alleles are present (i.e. homozygous G1/G1, homozygous G2/G2, or heterozygous G1/G2) [34]. Twelve to thirteen percent of African Americans carry two risk alleles [35]. Interestingly, APOL1 is not physiologically necessary and is absent in other primates and certain populations of humans [34, 36]. However, it has been shown that APOL1 can insert itself as a pore into the lysosome of *Trypanosoma* spp., a genus of parasite associated with the deadly disease African sleeping sickness, leading to swelling and parasite lysis [37, 38]. The G1 and G2 variants of the APOL1 seem to provide broader protections to certain strains of the *Trypansoma* spp. [39]. This likely provided a survival benefit to the ancestors of its carriers and thus explains its high prevalence today.

The mechanism by which APOL1 leads to kidney disease is incompletely understood. Lan et al. showed that APOL1 can induce podocyte injury by increasing

Table 7.1 Genetic mutations associated with development of FSGS [13, 24–28]

Gene	Product affected	Site of abnormality	Inheritance
NPHS1	Nephrin	Slit diaphragm	AR
NPHS2	Podocin	Slit diaphragm	AR
CD2AP	CD2-associated protein	Slit diaphragm	AR
ACTN4	Alpha actinin-4	Podocyte cytoskeleton	AD
MYO1E	Non-muscle myosin-IE	Podocyte cytoskelton	AR
MYH9	Non-muscle myosin-IIA	Podocyte cytoskeleton	AD
INF2	Inverted formin-2	Actin organization	AD
ARHGDIA	Rho GDP-dissociation inhibitor 1	Actin dynamics, signaling with Rho GTPase	AD
TRPC6	Transient receptor protein calcium channel 6	Podocyte ability to react to stimuli	AD
PTPRO	Receptor tupe tyrosine-protein phosphatase O	Podocyte to podocyte signaling	AR
PLCε1/NPHS3	PLCε1	Podocyte signaling and development	AR
SCARB	Scavenger receptor class B member 2	Putative lysosomal receptor	AR
LAMB2	Laminin beta 2	GBM to actin cytoskeleton interaction	AR
CD151	Tetraspanin	GBM and podocyte interaction	AR
WT-1	Wilm's tumor protein 1	Podocyte development	AD
LMX1b	LIM homebox transcription factor 1β	Podocyte and GBM development	AD
ITGB4	B4-integrin	Adhesion to cell-matrix	AR
SMARCAL1	SNF-related matrix associated actin-dependent regulator of chromatin subfamily A-like protein 1	Gene transcription	AR
MTTL 1	Mitochondrially encoded tRNA leuine 1	Mitochondrial tRNA	Maternal
COQ2	Polyprenyltransferase	Coenzyme Q10 biosynthesis	AR
COQ6	Ubiquinone biosynthesis monooxygenase COQ6	Ubiquinone biosynthesis	AR
PDSS2 [24]	Decaprenyl diphosphate synthase subunit 2	Decaprenyl tail of coenzyme Q10 production	AR
ADCK4 [25]	AarF domain-containing protein kinase 4	Coenzyme Q10 modulation	AR

AR = autosomal recessive; AD = autosomal dominant

lysosomal membrane permeability leading to swelling in a viral infection model and that the podocyte injury was particularly dramatic in HIV infected cells with the G1 or G2 variants [40]. Additionally, these researchers showed that media from the G1 and G2 variants can induce injury in non-infected podocytes, suggesting a secreted substance from the G1 and G2 variants as an additional means of injury [40].

Despite a seemingly strong association with FSGS and the variant alleles of APOL1, individuals with two APOL1 risk alleles only have a 4 % estimated lifetime risk of developing CKD. However, in the setting of two risk alleles and untreated HIV, the lifetime risk increases by as much as 50 % [35]. Based on these findings, some have come to suggest an additional insult (or insults) is necessary for developing chronic kidney disease. Some have speculated that the coexistence of sickle cell trait may be one of the factors that lead to chronic kidney disease in this population but more studies are needed [41].

7.3.2 Drugs

In the 1970's, Rao et al. noted a correlation with heroin addiction and proteinuric kidney disease with FSGS morphology on kidney biopsy. This prompted the term heroin-associated nephropathy or HAN [42]. In present times however, HAN has become uncommon, presumably due to the improved purity of heroin [2, 43]. It has been theorized that since HAN was more commonly observed in African American individuals, it may have some relation to APOL1 risk-variants [44]. Cases of FSGS occurring in bodybuilders who had used anabolic steroids for a prolonged period have also been reported and may be related to increased muscle mass leading to adaptive glomerular changes (which will be discussed later) and/or a toxic effect of the steroids themselves [45].

Non-illicit drugs have been associated with FSGS as well. Pamidronate, a bisphosphate that works on osteoclasts through multiple mechanisms including modulation of the actin cytoskeleton, may also affect the podocyte actin cytoskeleton given its associated with the collapsing variant of FSGS [2]. Interferon alfa, beta, and gamma all have effects on podocytes and when used exogenously for treatment, can induce FSGS as well. A nephrotic syndrome associated with lithium has been reported in case studies. Although the histology associated with lithium use is most often consistent with minimal change disease, FSGS has also been reported [46].

In kidney transplants, sirolimus (rapamycin), an mTOR inhibitor, has been associated with proteinuria and an FSGS pattern. Vollenbröker et al. showed that sirolimus can alter the expression of slit diaphragm proteins nephrin, TRPC6, and other proteins which are needed for podocyte adhesion and motility [47]. The impaired expression of these proteins has been associated with a FSGS pattern of injury (see above under genetic causes). Calcineurin inhibitors have been cited as having an association with collapsing FSGS in kidney allografts, possibly through their vasoconstrictive effects [2]. However, the occurrence of collapsing FSGS in kidney allografts is relatively uncommon despite the wide use of calcineurin inhibitors.

Additionally, the case series of collapsing FSGS in transplant recipients suggest a diverse array of causes, including immune complex deposits, and the characteristics of the donors, who might have had a predisposing risk factor such as *APOL1* risk alleles [48–50], were not mentioned.

7.3.3 Infectious

HIV-associated nephropathy (HIVAN) has been associated with collapsing FSGS, particularly among African American individuals with two *APOL1* risk alleles [35]. HIV RNA and circular viral DNA have been detected in renal glomerular and tubular epithelial cells from kidney biopsies [51] but HIV is unable to replicate once internalized by the podocyte [52]. In mouse models, expression of certain HIV genes can induce podocyte and renal tubular epithelial cells to dedifferentiate leading to proteinuria and collapsing FSGS histology [53–55].

Infections with cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19 have also been reported to cause collapsing FSGS. However, they are less common and their mechanism of injury is not as well characterized [56].

7.3.4 Adaptive Response

Focal segmental glomerulosclerosis can develop over time as a result of reduced renal mass or hemodynamic changes that lead to a maladaptive scarring (for causes see Table 7.2 [1]). The mechanism for the disease initially results from increased glomerular capillary pressure.

In animal models, when a significant portion of kidney is removed there is a vasodilation in both the afferent and efferent arterioles causing increased glomerular blood flow [57, 58]. Since the reduction in vascular resistance is disproportionally more in the afferent arterioles, inter-glomerular hypertension develops due to the rise in glomerular hydrostatic pressure [2]. This results in each remaining

Table 7.2 Etiologies for adaptive causes of FSGS

Reduced renal mass	Hemodynamic stress
Very low birth weight	Prolonged hypertension
Oligomeganephronia	Vaso-occlusive disease
Unilateral renal agenesis	Atheroembolic disease
Surgical nephrectomy	Obesity-related
Surgical excision or ablation	Increased lean body mass
Cortical necrosis	Cyanotic heart disease
Unilateral renal atrophy	Sickle cell disease
Reflux nephropathy	

nephron hyper-filtrating and thus compensating in an attempt to maintain overall glomerular filtration rate [58]. The glomerular hypertension leads to an increase in glomerular volume which is not accompanied by any increase in podocyte number. The podocytes, which become strained since they cannot readily divide to cover the expanded area, hypertrophy and detach from the basement membrane resulting in proteinuria and sclerosis (see below under common pathway for more details) [58].

In cases where there is increased hemodynamic stress (see Table 7.2), the mechanism is similar in that glomerular hypertension develops leading to glomerular hypertrophy, podocyte defects or detachment, and sclerosis. Both morbid obesity and an elevated lean body mass have been reported to cause an FSGS pattern of injury secondary to glomerular hypertension [1].

It is important to note that other diseases that affect the podocytes and glomerulus can have a focal and segmental pattern of glomerulosclerosis. Diabetic nephropathy, IgA nephropathy, membranoproliferative glomerulonephritis, post-infectious glomerulonephritis, pauci-immune glomerulonephritis, tubulointerstitial diseases, thrombotic microangiopathy, Alport's disease, and hypertensive nephrosclerosis have all been noted to have features that can resemble FSGS depending on the stage [3, 59, 60].

7.4 Pathology

7.4.1 Common Pathway Leading to Podocyte Injury

As previously mentioned, the causes of FSGS may be diverse, but it is believed they share a common pathway that leads to the characteristic pattern of injury. Podocytes have an actin cytoskeleton which enables podocytes to move their foot processes in response to mechanical or chemical stimuli. In FSGS, an insult or a genetic defects causes the podocytes to detach its foot processes from the glomerular basement membrane (also known as foot process effacement). With the effacement of the foot processes, the glomerular filtration barrier is compromised leading to loss of selectivity and proteinuria [61]. If the injury or abnormality persists, it leads to further effacement until the podocyte separates from the basement membrane and subsequently dies. The foot processes of podocytes not only act as a filter but also interdigitate with other podocytes forming a complex network for signaling. As an individual podocyte dies, the remaining podocytes are affected by its loss. The surviving podocytes hypertrophy to cover the denuded area leading to further foot process effacement and stripping of the basement membrane [62]. Additionally, death of a single podocyte may promote death of neighboring podocytes due to exposure to toxic factors (such as angiotensin II or tumor growth factor β) which are released by the dying podocyte, the loss of supporting factor previously produced by the podocyte (such as nephrin or vascular endothelial growth factor), increased mechanical strain, or a combination of all of these.[2, 63–66]. This pattern of propagation has been describe as a "domino-like effect" because the death of one podocyte seems to lead to death of additional podocytes [2].

The parietal epithelial cells from Bowman's capsule migrate to the stripped basement membrane as a possible reparative mechanism [67, 68]. However, the interaction of the basement membrane and parietal epithelial cells can create adhesions between the capsule and the basement membrane. These adhesions can then progress to sclerosis [68, 69]. Since this injury and apoptosis are localized to adjacent cells, it is not uncommon for lesions to appear segmental early in the disease course and then become more widespread as the disease progresses. Wharram et al. demonstrated in transgenic rats that once >40 % of podocytes are involved, the hallmark clinical features of severe proteinuria and renal insufficiency develop. However, they noted that significant proteinuria can develop with fewer podocytes being involved [70].

As more podocytes are afflicted, the sclerosis spreads through the glomerulus resulting in more capsular adhesions. These adhesions are believed to alter glomerular filtrate which may cause tubular simplification, interstitial injury, and eventual fibrosis [68]. These adhesions may also act as a bridge for peri-glomerular fibroblasts to migrate into the glomerular tuft and cause more glomerulosclerosis [68].

As more nephrons become affected, the renin-angiotensin system becomes more active. This leads to formation of angiotensin II which can promote podocyte apoptosis [71]. As more podocytes die, the remaining podocytes have increased protein uptake. The excessive protein uptake activates intracellular transforming growth factor-beta (TGFβ) [72] which can lead to endoplasmic reticulum stress, changing of the cytoskeleton, dedifferentiation, and apoptosis [73].

7.5 Histological Type

In 2004, Drs. D'Agati, Fogo, Bruijn, and Jennette proposed classifying FSGS into 5 categories (Cellular, Collapsing, Classic or not otherwise specified/NOS, Perihilar and Tip) based on the appearance on light microscopy to help with determining the potential etiology of the disease as well as improve accuracy of the diagnosis [74]. Though not universally accepted as definitive for diagnosis, certain variants can be associated with specific etiologies of FSGS. It is important to note that other primary glomerular disease such as diabetic glomerulosclerosis and chronic glomerulonephritis can have similar features to FSGS to the untrained eye. Therefore, it is important to take in all aspects of the biopsy and the clinical history before ascribing this pattern of injury to a specific entity. Please see Fig. 7.1 for histological images of each subtype and Table 7.3 for the details about the clinical features and potential clinic correlation of each subtype.

Immunofluorescence staining of FSGS normally shows coarse segmental IgM and C3 deposits at the sites of hylanosis, although deposits of C1 can also occur [2, 75]. It is important to stain for IgA since advanced IgA nephropathy can appear like FSGS with the only difference being the finding of mesangial IgA deposits in IgA nephropathy [76].

Electron microscopy plays an important role in the diagnosis of focal segmental glomerulosclerosis. Not only does it help rule out advanced depositional diseases

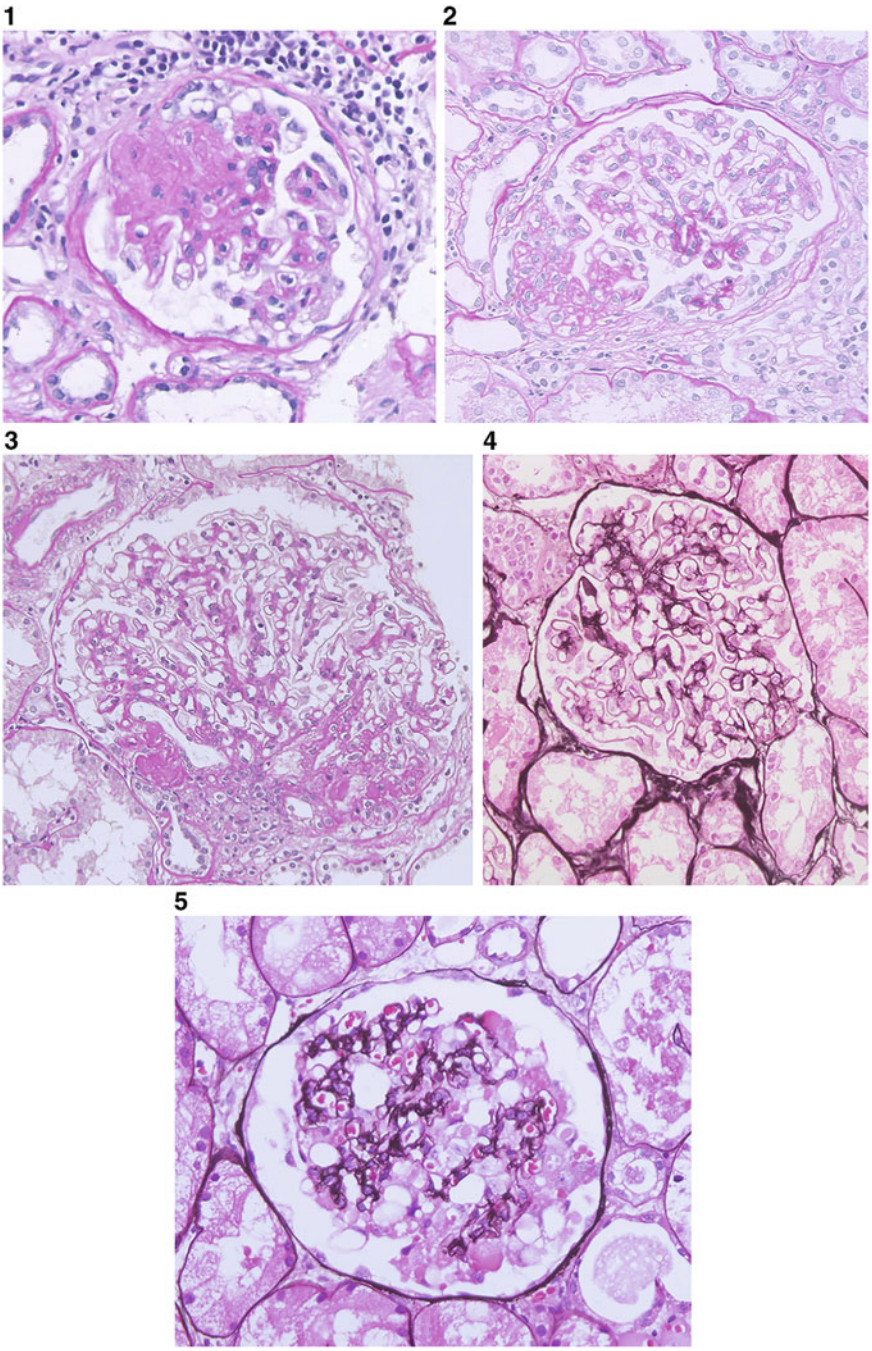

Fig. 7.1 Histologic variants of FSGS. (**1**) FSGS, NOS, PAS stain; (**2**) FSGS cellular variant, PAS stain; (**3**) FSGS, hilar variant, PAS stain; (**4**) FSGS, tip variant, Jones' silver stain; (**5**) FSGS, collapsing variant, Jones silver stain. All images are 400× magnification and are courtesy of Agnes B. Fogo, MD, Department of Pathology, Microbiology and Immunology, Vanderbilt University

Table 7.3 Classification, histology, and clinical features of variants of focal segmental glomerulosclerosis [2, 13, 52–58, 60]

Variant [74]	Major features [3, 73]	Clinical characteristics [2]	Associated causes [2]	Prognosis [75–78]
Cellular	– Increased cellularity of segments of endocapillary loops (endocapillary proliferation) resulting in collapsed lumina – Can have hylanosis	– Rarest variant – Usually presents with nephrotic syndrome – Believed to be an early stage in sclerosis formation	– Most commonly associated with the idiopathic cause but can be seen with secondary causes	– Fair – Remission ≥ progression to ESRD
Collapsing	– Shrunk glomerular tuft in relation to bowman's capsule – Podocyte hyperplasia and hypertrophy – *No* increased intracapillary cellularity or matrix – Can be segmental or global	– Highest prevalence in Black race – Nephrotic syndrome with massive proteinuria	– Can be seen with idiopathic – Most often related to viral, medication or vascular disease	– Very poor – Remission ≪ progression to ESRD
"Classic" or not otherwise specified (NOS)	– Segmental glomerular capillary collapse – Increased matrix –All other types must be excluded	– Most common variant – Variable level of proteinuria	– Can be seen with all etiologies of disease – Other variants and diseases can evolve into this types over time	– Fair to poor – Remission ≤ progression to ESRD
Perihilar	– Sclerosis and hylaninosis near glomerular cleft of vessels (hilum)	– Typically, sub-nephrotic proteinuria	– Often result of adaptive changes (i.e. reduced renal mass, increased body mass)	– Poor – Remission < progression to ESRD
Tip	– Limited to outer 25 % of glomerular tuft – Must have adhesion or podocytes attached to parietal or tubular cells – Must *not* have perihilar sclerosis	– More common in Caucasians – Abrupt onset of nephrotic syndrome	– Most often seen in idiopathic disease	– Best – Remission ≫ progression to ESRD

but it can also suggest the etiology of the disease. Deegens et al. have proposed that foot process width greater than 1500 nm is sensitive and specific for primary FSGS [77]. Though some have suggested that biopsies with a higher percentage of foot process effacement are associated with primary/idiopathic FSGS, studies looking at percentage of foot process effacement showed no statistical difference between those with primary/idiopathic FSGS and those with a secondary form. However, these studies were small and likely underpowered for this statistical analysis [75, 77]. Therefore, the percentage of foot process effacement can be helpful when used in conjunction with other clinical and histologic data [4].

7.6 Clinical Features

7.6.1 Epidemiology

Several studies have suggested an increased incidence of focal segmental glomerulosclerosis in both children and adults around the world over the last few decades [1]. Some of these studies have shown a steady increase in the incidence of FSGS since the 1970's and that FSGS has now become the leading cause for primary glomerulonephritis in countries like Brazil [78–82]. However, studies out of the UK and Korea suggest a relative constant incidence of FSGS during a similar period of time [83, 84]. The reason for the increased incidence among some populations, while not among others, has yet to be explained.

In the US, the rate of ESRD from FSGS has increased by 11 fold over a 21 year period, especially among black individuals [85]. Even among a predominately Caucasian population, there was a 13-fold increase in biopsies with FSGS between 1974 and 2003 [86]. Some have speculated that part of the increase may be related to changes in disease classification and biopsy practices but it is generally accepted the prevalence of FSGS is on the rise. Primary FSGS is more common among males, who also have a 1.5 to 2-fold higher risk of progressing to ESRD, compared to females [85]. Black individuals have a higher incidence of FSGS compared to Caucasians, both in childhood and adulthood [1].

7.6.2 Presentation

Individuals with FSGS can have a mixture of presenting features. Classically, primary or idiopathic FSGS in adults present as having nephrotic syndrome (defined as proteinuria > 3–3.5 g/day, serum albumin < 3.5 g/dl, and peripheral edema). Hypertension, microscopic hematuria, and elevated serum creatinine can also occur but these have been reported to occur less frequently [59, 87]. However, depending on the underlying cause, severity, and the stage of the disease, individuals can present with sub-nephrotic proteinuria, preserved serum albumin, minimal to no

peripheral edema, and normal serum creatinine [1]. Some have suggested that the lack of nephrotic syndrome and sub-nephrotic range proteinuria is more indicative of a secondary form of FSGS [4, 59].

7.6.3 Prognosis

The prognosis of FSGS is quite variable which is likely related to the diversity of causes. In general, compared to other glomerular diseases, such as minimal change disease, the rate of spontaneous remission is uncommon (approximately 5–23 % depending on the study) [88, 89]. There have been a few features that have been suggestive of overall risk of developing end-stage renal disease (ESRD). One factor that has been associated with worse outcomes over several decades is the degree of proteinuria [88–93]. Comparatively, patients with sub-nephrotic range proteinuria have less than a 15 % chance of progression to ESRD at 10 years while nephrotic patients have an approximately 50 % chance of ESRD at 5–10 years [59, 88]. An even worse outcome was observed in individuals with "massive proteinuria" (defined as >10–14 g of protein/day). Patients with massive proteinuria progressed to ESRD within 2–3 years on average [59, 93]. An important caveat to proteinuria as a prognostic indicator is the individual's response to therapy. In the study by Rydel et al., patients with nephrotic range proteinuria who obtained a complete remission (defined as less than or equal to 0.25 g of proteinuria/day) or a partial remission (defined as 0.26–2.5 g of proteinuria/day) had approximately the same rate of renal survival as those with sub-nephrotic proteinuria at 10 years. Additionally, nephrotic patients who either received no treatment or did not respond to treatment had comparable renal outcomes at 10 years [88]. Similarly, Stirling et al.'s study out of the UK reported a 94 % rate of dialysis-free survival for patient who had either a complete or partial remission compared to 53 % for those who did not achieve remission ("non-responders") at 5 years [89]. It is important to note that in Troyanov et al.'s study looking at a predominately white population with FSGS, patients who achieved a partial remission had worse renal survival compared to those who had complete remission, but still had markedly better outcomes than non-responders [87].

As mentioned above, the histological sub-type of FSGS can provide some prognostic value. In general, it is believed the tip variant has the best outcome with treatment while the collapsing variant is associated with the worst outcome [94]. The perihilar type is most often caused by an adaptive change which tends to have lower amounts of proteinuria [2, 95]. Once the disease reaches nephrotic range proteinuria, it is often associated with more advanced fibrosis and sclerosis and thus lower chance of achieving remission [95]. Regardless of histological type, patients who failed to achieve any type of remission overall have worse outcomes [95, 96].

It has been reported that individuals of black race have a worse prognosis [1, 2] but this has not been the outcome in all studies [87, 88, 97]. The reason for the seemingly worse outcomes among black individuals may be related to the pathologic subtypes. There is a higher incidence of the collapsing variant and lower incidence

of the tip variant compared to white patients and thus black patients have a lower probability of achieving remission [95]. When comparing outcomes of patients with collapsing FSGS, there was reportedly no statistical difference in risk of progression to ESRD based on race [98].

The amount of sclerosis and fibrosis at time of biopsy, which often indicates more advanced disease, has been shown to be associated with worse outcomes [59]. It is important to note that studies showing worse outcomes among the collapsing variant also noted more glomerular sclerosis and interstitial fibrosis at time of biopsy [95, 98]. Renal insufficiency at time of biopsy has also been reported to be associated with lower rate of remission and worse outcomes [1, 59, 87, 98, 99]. Schwartz et al.'s multivariate analysis found a serum creatinine > 1.3 mg/dl at presentation was associated with a 10.7 relative risk for progression to ESRD in all patients. Among nephrotic patients, there was 12.7 relative risk increase for progression to ESRD when there creatinine was >1.3 mg/dl, which was more strongly correlated with ESRD than interstitial fibrosis ≥20 % (RR 6.57) [99].

7.6.4 Treatment

Treatment can be challenging in the clinical setting since the ultimate cause of FSGS may be difficult to determine and the best treatment option should ideally be tailored to the cause. Figure 7.2 outlines an algorithm to help determine appropriate treatment [2, 4].

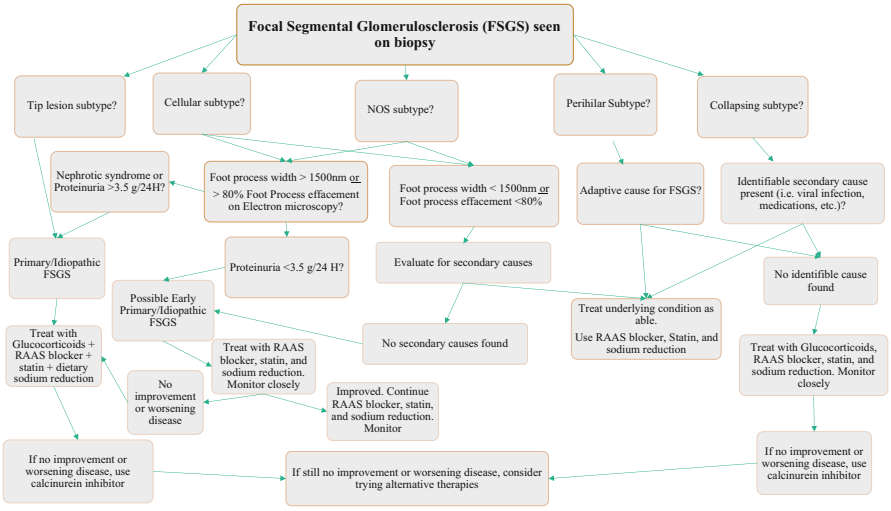

Fig. 7.2 Algorithm for diagnosis and treatment of FSGS

7.6.4.1 Conservative Management

At present, there are no large, randomized trial data on the use of renin-angiotensin-aldosterone system (RAAS) blockade in patients with FSGS. The recommendation to use RAAS blockade in FSGS is largely based on data from other proteinuric kidney diseases. It is important to note that these studies on average had patients with sub-nephrotic range proteinuria and very few patients with a diagnosis of FSGS. Furthermore, many of these trials excluded patients with massive (>10 g/24 h) proteinuria and/or those being treated with immunosuppression [60, 100]. In a prospective cohort study, angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use seemed to provide a renal survival benefit but this did not meet statistical significance in multivariate analysis [87]. However, given the paucity of high quality data in FSGS and the relatively strong data for their use in other proteinuric kidney disease, RAAS blockade is generally recommended in patients who do not have contraindications for their use.

Similarly, blood pressure goals for patients with FSGS have not been defined by randomized trial data. The recommendations on treatment of FSGS is largely based on data from other proteinuric kidney diseases and observational data suggesting those with higher blood pressure tended to have worse outcomes [91]. However, on multivariate analysis of prospective data, lower MAPs were not associated with renal survival [87]. Thus, BP goals are extrapolated from KDIGO recommendations to treat blood pressure to goal of <130/80 in all chronic kidney disease patients and target a goal of <125/75 in those with more than a gram of proteinuria [101]. KDIGO's guidelines also recommend lifestyle modifications including sodium reduction, normalization of weight, and smoking cessation [101].

It is felt that patients with the secondary types of FSGS derive the most benefit from conservative management strategies since secondary FSGS is often the result of maladaptive glomerular hypertension and is not likely to respond to immunosuppression therapy.

7.6.4.2 Immunosuppression

Corticosteroids Oral corticosteroid therapy has become the first-line therapy for most individuals with idiopathic FSGS and generally given at a dose of 1 mg/kg/day of prednisone for 2–3 months with a slow taper over another 4 months [102]. However, the majority of data supporting the use of oral corticosteroids for FSGS comes from nonrandomized, retrospective series [60]. Many of these studies differed in dosing of steroids, duration of treatment, and the definition of complete and partial remission. The only randomized, prospective (open label) trial of steroids in FSGS was conducted by Nayagam et al. In this trial, 16 adults were randomized to prednisolone 1 mg/kg/day for 3–6 months followed by a taper and 17 participants were randomized to mycophenolate mofetil (MMF) and low dose prednisone. Complete or partial remission was observed in 69 % of patients in the prednisolone group and 71 % in the MMF + prednisolone group [103]. Oral steroids have not been

shown to be superior to RAAS inhibition in all trials. A single center retrospective cohort by Stiles and colleagues looked at 22 patients with FSGS that had proteinuria greater than or equal to 3 g/24 h who were treated either with steroids for 4 months at a dose of approximately 1 mg/kg/day and ACEi versus conservative management with ACEi and statin therapy alone. Neither group of patients achieved complete remission and the rate of partial remission and progression to ESRD was similar between the two groups [104].

Alternatives to Steroids The use of high dose steroids is often problematic in those with diabetes, osteoporosis or prolonged previous use of corticosteroids. Unfortunately, data using other agents such as calcineurin inhibitors (CNIs) or MMF as the initial agent to treat FSGS are scarce. There is only one trial of tacrolimus (a calcineurin inhibitor) as initial therapy for FSGS. In this trial, 6 adults were treated with tacrolimus (to achieve a mean trough level of 5.5 ng/ml) for ~13 months [105]. All 6 patients achieved a partial remission (mean time to remission of 6.5 months). All participants remained on tacrolimus for the duration of the study. Thus, the optimal duration of CNI therapy for initial treatment of FSGS remains unknown. Since CNIs cause vasoconstriction, they should not be used in those with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, in those with a rapidly rising creatinine or in individuals with moderate to severe fibrosis on renal biopsy. CNIs should be used with caution in those with moderately reduced eGFR and the serum creatinine should be monitored closely. Data on MMF or mycophenlic acid as initial treatment of FSGS are also scarce. As mentioned above, Nayagam et al., have used MMF in conjunction with prednisolone for initial therapy [103].

Relapse Unfortunately, relapse after treatment is common in FSGS [60]. In the study by Troyanov et al., over a median follow-up of 65 months, 55 of 281 subjects had a complete remission and 117 had a partial remission [87]. The cumulative relapse rate was 47 %. There are no controlled trials examining the optimal treatment of FSGS after relapse. Many clinicians will use a repeat course of steroids if the initial course was well tolerated. Options for individuals who cannot tolerate a repeat course of steroids include CNIs (if no contraindications exist to CNI use) and MMF.

Steroid-Dependent FSGS Individuals are deemed steroid-dependent if they relapse duing tapering of oral steroids or shortly after treatment. Data on the optimal approach to treating steroid-dependent FSGS are limited. Calcineurin inhibitors can be used if patients have preserved kidney function and little fibrosis on renal biopsy. Published data on the use of CNIs for steroid-dependent nephrotic syndrome often include patients with minimal change disease. Nonetheless, the use of CNIs in steroid-dependent nephrotic syndrome has been shown to induce remission rates of 70–80 % at 12 months [60]. Other options include the use of alkylating agents such as cyclophosphamide. Ponticelli et al. assigned 77 patients with steroid-dependent nephrotic syndrome (some of whom had FSGS) to oral cyclophosphamide 2.5 mg/kg/day for 8 weeks or cyclosporine 5 mg/kg/day for adults and 6 mg/kg/day for children for 9 months, tapered by 25 % per month until discontinuation by month 12. Rates of

remission were similar between the two groups but at 2 years significantly more patients in the cyclophosphamide group had not had any relapse of nephrotic syndrome [106]. Rituximab has also been used for steroid-dependent nephrotic syndrome but its use in the treatment of FSGS needs additional investigation.

Steroid-Resistant FSGS Individuals with steroid-resistant FSGS have persistent nephrotic syndrome despite treatment with oral prednisone (1 mg/kg/day or 2 mg/kg every other day) for 4 months. Steroid resistance is thought to occur in 40–60 % of individuals with FSGS and is associated with a significantly increased risk of progression to ESRD. As in the case of steroid-dependent FSGS, there are few trials that focus specifically on the treatment of steroid-resistant FSGS. Cattran et al. randomized 49 adults with steroid-resistant FSGS and eGFR > 42 ml/min/1.73 m^2 to cyclosporine + low dose prednisone versus placebo + low dose prednisone for 26 weeks [107]. At 26 weeks, 75 % of the cyclosporine group versus 22 % of the placebo group had a partial or complete remission of proteinuria. Among patients that had a remission, relapse occurred in 43 % of the cyclosporine group and 40 % of the placebo group by week 52.

MMF has been used to treat steroid-resistant FSGS in the National Institutes of Health (NIH) Focal Segmental Glomerulosclerosis Clinical Trial. In this study, 138 children and young adults with steroid-resistant FSGS were randomized to prednisone (up to 15 mg/day) + cyclosporine or MMF/dexamethasone pulses for 12 months [108]. No significant difference in rates of cumulative remission was seen between the two groups. This study, however, may not be widely applicable to the treatment of FSGS as the definition of steroid-resistance was the presence of proteinuria after only 4 weeks of steroid treatment, the trial included a large number of children, several patients in each group had sub-nephrotic proteinuria, and dexamethasone is not widely used in the treatment of nephrotic syndrome.

Alkylating agents have been used in one small trial of steroid-resistant or steroid-dependent patients with nephrotic syndrome [109] but the remainder of data on the use of cyclophosphamide for steroid-resistant FSGS comes from observational studies. Rituximab, a monoclonal antibody against CD20, has also been used for steroid-resistant FSGS in a few small trials. Gulati et al. treated 33 patients with steroid-resistant or steroid-dependent nephrotic syndrome with rituximab [110]. Six months after treatment, 49 % of patients had a partial or complete response and 51 % has no response. After a mean of 21 months of follow up, 15 patients had a sustained complete or partial remission.

Adrenocorticotropic hormone (ACTH) has also been used for the treatment of FSGS. A case series by Hogan et al. reports the use of ACTH gel in 24 adults, most of whom had steroid-resistant or steroid-dependent FSGS [111]. There were 5 partial and 2 complete remissions with 2 patients experiencing relapse during the 66 month follow up period. Drawbacks to ACTH use include the high cost and the development of side effects seen with high-dose steroids.

Recurrence After Transplantation The risk of FSGS recurrence after transplantation is estimated to be between 30 % to 50 % [112]. Recurrence of massive proteinuria soon

after transplantation is thought to be due to a permeability factor and is often treated with plasma exchange. Cyclophosphamide has been tried with variable success to treat recurrence in the allograft and rituximab has also been used. Abatacept, an antibody against the T cell costimulatory molecule CD80 (B7-1) has also been used in a small trial which included patients with FSGS recurrence after transplantation [113]. CD80 upregulation in the podocyte leads to downregulation of β1 integrin. Thus abatacept is thought to stabilize the podocyte by increasing β1 integrin expression.

Current Trials Current clinical trials investigating treatments for FSGS include comparing sparsentan (a dual endothelin receptor antagonist and ARB) with irbesartan (ARB), using adalimumab (a tumor necrosis factor α (TNFα) inhibitor), using an antibody against transforming growth factor β (TGFβ), and studies using rituximab. Details of current clinical trials in FSGS can be found at the ClinicalTrials.gov website (https://www.clinicaltrials.gov/ct2/results?term=fsgs&Search=Search).

7.7 Summary

FSGS is due to multiple causative factors that damage podocytes, ultimately leading to podocyte death and scarring of the glomerulus. There are few uniformly effective treatments for FSGS but as understanding of this heterogenous group of diseases increases, tailored, more effective therapeutics are likely to be developed.

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