CKJ REVIEW

Challenges in primary focal segmental glomerulosclerosis diagnosis: from the diagnostic algorithm to novel biomarkers

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ABSTRACT

Primary or idiopathic focal segmental glomerulosclerosis (FSGS) is a kidney entity that involves the podocytes, leading to heavy proteinuria and in many cases progresses to end-stage renal disease. Idiopathic FSGS has a bad prognosis, as it involves young individuals who, in a considerably high proportion (~15%), are resistant to corticosteroids and other immunosuppressive treatments as well. Moreover, the disease recurs in 30–50% of patients after kidney transplantation, leading to graft function impairment. It is suspected that this relapsing disease is caused by a circulating factor(s) that would permeabilize the glomerular filtration barrier. However, the exact pathologic mechanism is an unsettled issue. Besides its poor outcome, a major concern of primary FSGS is the complexity to confirm the diagnosis, as it can be confused with other variants or secondary forms of FSGS and also with other glomerular diseases, such as minimal change disease. New efforts to optimize the diagnostic approach are arising to improve knowledge in well-defined primary FSGS cohorts of patients. Follow-up of properly classified primary FSGS patients will allow risk stratification for predicting the response to different treatments. In this review we will focus on the diagnostic algorithm used in idiopathic FSGS both in native kidneys and in disease recurrence after kidney transplantation. We will emphasize those potential confusing factors as well as their detection and prevention. In addition, we will also provide an overview of ongoing studies that recruit large cohorts of
INTRODUCTION

Focal and segmental glomerulosclerosis (FSGS) is a histological pattern used in clinical practice to define a podocytopathy that develops with nephrotic-range proteinuria and segmental obliteration or collapse of glomerular capillary loops with increased extracellular matrix in some glomeruli. FSGS is the leading glomerulopathy responsible for end-stage renal disease (ESRD) in the USA [1]. It is the cause of ~40% of the nephrotic syndrome in adults and 20% in children [2]. As in other kidney diseases, the incidence of FSGS is generally 1.2- to 1.5-fold higher in men than in women [3]. FSGS can be classified into two main forms: secondary, which includes genetic, adaptive, infection/inflammation and medication-associated FSGS, and primary or idiopathic FSGS [2, 4]. Primary FSGS is thought to be caused by an unknown circulating factor(s) that damages the podocytes and consequently permeabilizes the glomerular filtration barrier [2]. The major concerns of idiopathic FSGS are the poor renal prognosis with an absence of response to immunosuppressive therapies or relapses and its recurrence after kidney transplantation in ~30–50% of patients, which often leads to renal graft failure [5].

Primary FSGS should be suspected in patients with abrupt nephrotic proteinuria, severe hypoalbuminemia, oedema and uniform podocyte foot process effacement (FPE) by electron microscopy (EM) of a renal biopsy [6]. A careful and detailed medical history and clinical examination are needed, as often it is not easy to distinguish between primary and secondary FSGS. From a practical point of view, it is worth mentioning that primary FSGS is often confused with other glomerulopathies such as minimal change disease (MCD). In fact, many authors believe that MCD and primary FSGS are the same disease, the second being a more advanced stage of the first, where glomerular lesions can be seen by light microscopy (LM) [7]. Diagnosis of primary FSGS is not a straightforward process and therefore several studies have focused on finding factors and markers that may be helpful for diagnosis of the disease and the detection of FSGS recurrence after kidney transplantation [8–10].

In this review we discuss the diagnosis algorithm of FSGS in the native kidney and its relapse after kidney transplantation. In addition, we will review studies focused on new biomarkers for early diagnosis and/or detection of FSGS relapse after kidney transplant. We will also cover new strategies aimed at identifying accurate biomarkers of disease activity and progression.

The primary FSGS diagnosis in the native kidney

FSGS is a histological term rather than a specific clinical disease. FSGS is a lesion resulting from a podocyte injury characterized by segmental (in parts) and focal (of some) sclerosis of the glomeruli. Thus the histological finding lends its name to the associated clinical disease. It can be classified into secondary FSGS or primary (idiopathic) FSGS. Secondary FSGS lesions are observed as an adaptive response to a reduction in nephron mass, genetic mutations, drug consumption or viral infections, among others (Table 1) [4]. In secondary FSGS cases (except for the genetic forms), treatment of the underlying cause of the disease can reverse or slow down the progression of the disease, depending on the extent of established renal damage (i.e. angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment for hypertension-caused FSGS or antiviral treatment for virus-induced FSGS). In contrast, primary FSGS is thought to be caused by undefined circulating factors that cause abnormal glomerular permeability and is diagnosed after exclusion of any other identifiable cause of secondary FSGS [4]. This subtype of FSGS is associated with a poor renal prognosis when compared with secondary forms [12] and another primary glomerulonephritis [13] and requires immunosuppressive treatment. Therefore the distinction between primary and secondary forms of FSGS has therapeutic and prognostic implications. As the presence of an FSGS lesion itself in a kidney biopsy does not offer a precise diagnosis, it remains a clinical diagnosis. Additionally, other diseases may present similar clinical and histological findings, such as MCD or focal and global glomerulosclerosis (FGGS). Identifying each form properly is crucial to avoid unnecessary immunosuppressive-based therapeutic approaches and to establish the appropriate treatment for the FSGS patient.

FSGS is clinically noticed when patients present with heavy proteinuria. Depending on the degree of proteinuria, primary or secondary FSGS can be suspected. Patients with primary FSGS usually present with nephrotic-range proteinuria (> 3.5 g/day) with complete nephrotic syndrome (severe hypoalbuminemia), often associated with renal insufficiency, hypertension and microhaematuria [14]. In contrast, secondary FSGS patients usually present a broad range of proteinuria (including subnephrotic and nephrotic range) and in general do not develop complete nephrotic syndrome despite the presence of nephrotic-range proteinuria. Renal insufficiency is less common in secondary FSGS and is usually associated with a slow increase of proteinuria over time [15]. However, this is not applicable for genetic FSGS, which may be very aggressive, with early-age onset, even in utero, associated or not with extrarenal characteristic clinical features, with overall progression to ESRD [16].

Together with clinical and laboratory findings, kidney biopsy is key for disease identification. However, histological injury is difficult to evaluate in single kidney sections since the focal sclerotic lesions, which are present in many glomeruli, affect only 12.5% of the total glomerular volume [17]. Therefore it is essential to obtain representative biopsy specimens that include at least 10 glomeruli, both cortical and juxtamedullary, as sclerotic changes may occur earlier in the latter. Juxtamedullary glomeruli can sometimes be missed on the kidney biopsy. Furthermore, these samples should be processed in successive sections that allow observation of the whole glomerular tuft and evaluation in LM. The histology of FSGS is defined by a segmental increase of the mesangial matrix with obliteration of the capillaries, sclerosis, hyalinosis, segmental scarring and finally Bowman’s capsule adhesion to the glomerular tuft. Under LM, FSGS histological lesions can be classified into five subtypes according to the Columbia classification [18]: perihilar, tip,
collapsing, cellular and not otherwise specified (NOS). NOS is the most common form in diverse series [19]. Prognosis may also be associated with the histological subtype. The tip variant has shown the highest rates of remission, while the collapsing variant is related to poor prognosis [20]. Of note, initial stages are only detectable by electronic microscopy where a degree of diffuse podocyte FPE should be observed. Generalized diffuse FPE (>80% of the analysed podocitary surface) can be associated with primary FSGS or MCD, while segmental and <80% FPE is usually related to secondary FSGS [21, 22]. FPE assessment using transmission electronic microscopy is to date the only established way to analyse the podocyte morphology, but it is far from being a standard method, as it is technically complex, requires ability and time and, moreover, deals with a geometric bias derived from physical sectioning [23]. Therefore, novel high-resolution microscopy techniques are in development to improve visualization of the glomerular filtration barrier compounds [23, 24].

When the onset of proteinuria with nephrotic syndrome is noted in paediatric patients, the diagnostic approach is very different. A kidney biopsy is discouraged as a first-line diagnostic procedure. When a child presents with proteinuria associated with nephrotic syndrome, treatment with steroids is started. The majority of patients are steroid-sensitive (~85%) [25, 26] and a kidney biopsy is normally not performed unless the patient develops steroid resistance. In case of steroid resistance, a kidney biopsy and genetic testing are indicated. About 15% of the paediatric patients with nephrotic syndrome are corticosteroid resistant and, of these, ~60% do not respond to any other therapeutic option. FSGS is detected in the kidney biopsy in >50% of steroid-resistant paediatric patients [26]. Moreover, most of the genetic forms of FSGS appear during childhood and are mainly associated with corticosteroid resistance. Mutations in the nephrin (NPHS-1), Wilms tumour 1 (WT-1) and podocin (NPHS-2) genes can explain ~70% of the studied cases of corticosteroid-resistant nephrotic syndrome [26]. Furthermore, routine whole-exome sequencing has allowed not only the description of >30 genes related to steroid resistance in nephrotic syndrome [11, 27, 28], but also discarding of other kidney diseases with proteinuria and FSGS, but from a totally different aetiology (i.e. Alport syndrome [29, 30], kidney dysplasia [31] or congenital abnormalities of the kidney and the urinary tract [32, 33]). A positive genetic test will focus the therapy on an antiproteinuric and symptomatic treatment, avoiding exposure to immunosuppression, but a negative result does not fully exclude mutations not previously reported.

Relapse of FSGS after kidney transplantation

One of the major concerns of primary FSGS is that the disease can recur after kidney transplantation and it seems to be related to the permeabilization activity of the FSGS circulating factor(s). Post-transplant FSGS recurrence happens in ~30–50% of patients and it can occur immediately or months to years after transplantation [5, 34]. The known risk factors for FSGS recurrence include younger patients, those who progress to ESRD within 3 years of diagnosis, a history of recurrence in a prior allograft and patients with higher proteinuria levels pre-transplantation [35]. Recurrent primary FSGS presents with nephrotic-range proteinuria and frequently has a rapid onset in the early post-transplant period. Patients usually have symptoms and signs of nephrotic syndrome, such as oedema, hypalbuminaemia and hyperlipidaemia, together with some degree of graft dysfunction. Nevertheless, the presence of proteinuria is enough to raise the suspicion of FSGS recurrence in patients that do not develop the full clinical picture. The definitive diagnosis is performed by allograft biopsy, where the characteristic features of FSGS are identical to FSGS in the native kidney, although in the initial phases the histological findings are characterized by a normal kidney under the optical microscope and podocyte FPE using EM [36]. The treatment for FSGS recurrence, as in native kidney idiopathic FSGS patients, is not standardized...
Table 2. Characteristics of various forms and diseases included in the differential diagnosis of FSGS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Primary FSGS</th>
<th>Secondary FSGS</th>
<th>Genetic FSGS</th>
<th>MCD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical history</strong></td>
<td>Acute onset of nephrotic syndrome without risk factors or previous renal disease history</td>
<td>Risk factors are present, such as obesity, drug consumption, vesicoureteral reflux, renal agenesis or reduced nephron mass or viral infection</td>
<td>Family history of FSGS disease (although frequently there are not familiar records); proteinuria or nephrotic syndrome with onset in early childhood or adolescence</td>
<td>Acute onset of nephrotic syndrome without risk factors or previous renal disease history</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td>Nephrotic syndrome: peripheral oedema, hypoalbuminaemia and &gt;3.5 g of proteinuria in 24-h urine; haematuria is common</td>
<td>Non-nephrotic or nephrotic-range proteinuria, without nephrotic syndrome; normal serum albumin levels</td>
<td>Childhood-onset genetic FSGS: usually nephrotic syndrome is present; adolescence or adult-onset genetic FSGS: proteinuria without nephrotic syndrome</td>
<td>More rapid onset of nephrotic syndrome; peripheral oedema, hypoalbuminaemia and &gt;3.5 g of proteinuria in 24-h urine</td>
</tr>
<tr>
<td><strong>Pathological findings</strong></td>
<td>LM: segmental areas of sclerosis, partial capillary collapse and hyaline deposits* IF: none or few immune deposits in sclerotic lesions positive to IgM and occasionally to C3 EM: usually diffuse (&gt;80%) podocyte FPE</td>
<td>EM: usually segmental (&lt;80%) podocyte FPE</td>
<td>EM: either diffuse or segmental podocyte FPE</td>
<td>LM: normal glomeruli</td>
</tr>
</tbody>
</table>

*Depending on the location of the lesions, tip and perihilar variants are distinguished. Cellular and collapsing variant show their own characteristics. If not a quality biopsy, glomeruli may seem normal. IF, immunofluorescence.

and the results are variable [37]. Kidney transplanted patients are usually already under a tacrolimus-based immunosuppressive treatment, therefore, to manage the FSGS recurrence, a change to cyclosporine can be performed as a strategy to decrease proteinuria [38]. Currently, early plasmapheresis treatment combined with intensified immunosuppression is the most common treatment choice for primary FSGS recurrence [39]. However, the results obtained with this treatment approach are variable and, in addition, these treatments are not exempt from toxicity [34, 40, 41].

De novo FSGS may also occur in the transplanted kidney among patients who did not have FSGS as a cause of ESRD in the native kidney. This is often detected >12 months after transplantation and is associated with variable amounts of proteinuria (including the nephrotic range), hypertension and progressive deterioration of renal allograft function. Compensatory glomerular hyperfiltration in residual nephrons caused by nephron loss or low nephron number in the transplanted kidney (size discrepancies between the graft and the recipient) has been implicated in the pathogenesis of de novo FSGS. Therefore hypertension, diabetes, allograft rejection, immunosuppressive-induced allograft damage, BK polyomavirus or parvovirus B19 infection and any other condition leading to a loss of renal mass can be involved in the pathogenesis of de novo FSGS [42]. De novo FSGS should be closely monitored in patients with unknown aetiology of ESRD in the native kidney, as primary FSGS recurrence cannot be totally excluded.

Despite features that allow us to discern primary FSGS and its relapses from other variants of FSGS and other renal diseases (Table 2), none of these findings is pathognomonic and identifying primary FSGS continues to be challenging. It is important to highlight again that FSGS is a histological pattern rather than a specific disease and that not all causes leading to podocyte damage have been elucidated. It is unknown whether primary FSGS is the consequence of one circulating factor or the conjunction of different factors that damage the glomerular filtration barrier. Furthermore, it is not clear what determines the response to immunosuppressive treatment and if there are different variants of primary FSGS. Finally, although genomic analysis has allowed the description of many genetic mutations related to FSGS, it is possible that still unidentified genetic alterations are responsible for adult FSGS onset, a fact that would lead to a mistaken diagnosis. For all these reasons, during the last decades, different groups have tried to find different biomarkers to help us recognize and understand the pathways involved in primary FSGS.

Towards a better understanding of FSGS

FSGS is a complex pathology not only because of the difficulties in diagnosis mentioned earlier, but also due to its low prevalence and the lack of clinical tools for its risk stratification, prediction of remission, treatment selection and monitoring of drug response. In addition, FSGS may show a slow progression, thus requiring years of follow-up to prove the effectiveness of an intervention. Therefore it has been necessary to join efforts and collect data from patients from different hospitals to obtain large cohorts to study the pathologic mechanism (among others) of FSGS and the response to different treatment approaches. Several registries have been created to this end, such as the Nephrotic Syndrome Study Network (NEPTUNE) and Cure Glomerulonephropathy (CureGN).

The NEPTUNE is a prospective observational study that began in 2010 and will recruit 450 paediatric and adult patients not only with FSGS, but also with MCD and membranous glomerulonephritis (MGN) at the time of the first renal biopsy clinically indicated for proteinuria. The enrolment includes 18 clinical centres in the USA and Canada and aims to find changes in urinary protein excretion and renal function and to assess the outcomes in life quality, development of new-onset
of the M-type phospholipase A2 receptor [68] and thrombospondin type-1 domain-containing 7A [69] as the target antigens in most patients with primary MGN, studies of galactose-deficient IgA1 and antiglycan response in IgAN [70] and associating mutations in apolipoprotein L1 to the development of kidney disease in patients of African ancestry [71, 72]. But although the number of genetic mutations identified in patients with FSGS has also expanded in the last decade [73], the causal mechanism of the primary FSGS form is still unknown. The registry data such as that obtained with the NEPTUNE or the CureGN cohorts will most probably provide a platform for genetic testing and the identification and validation of new biomarkers. These large studies may be helpful to better understand and manage primary FSGS as well as other glomerulonephritis.

**Novel biomarkers to diagnose primary FSGS**

As mentioned before, sometimes it is difficult to distinguish between different forms of FSGS and even to differentiate it from other glomerular diseases. The major challenge in FSGS diagnosis is early detection of the primary or idiopathic forms in order to decide the best therapeutic option. Several approaches have been used in order to improve our understanding of the disease and help in diagnosis and management (Figure 1).

As the disease is mainly a glomerular dysfunction, efforts have been made to establish which proteins are differentially expressed in glomerular cells of primary FSGS patients that could potentially be used as markers. In 2003, gene expression analysis of common podocyte proteins (ACTN4, GLEPP-1, WT-1, synaptopodin, dystroglycan, nephrin, podoplanin and podocin) of microdissected glomeruli suggested that the podocin:synaptopodin expression ratio may be useful to distinguish FSGS from MCD and nephrotic syndrome, although not from MGN [74]. CD44" staining in the glomerular parietal cells has also been related to FSGS. Although initially it seemed that it was specifically associated to primary FSGS forms [75, 76], it has also been detected in secondary forms [77], suggesting that CD44 expression in the parietal cells is related to a common FSGS development mechanism. Furthermore, kidney tissue microRNA (miRNA) expression has also been analysed in FSGS patients. Although several miRNAs are upregulated in glomeruli of primary FSGS patients [78], it seems that miRNA-193a is relevant for development of the disease, as it decreases the expression of WT-1, which compromises the podocyte function [79]. miRNA-193a is also increased in urinary exosomes of FSGS patients when compared with MCD patients [80], thus this miRNA could be suitable to detect primary FSGS, although this needs further validation.

Although study of the proteins specifically expressed in FSGS in the kidney tissue has helped in understanding the disease, to date the clue to better diagnose idiopathic FSGS has not been found. Therefore a specific non-invasive biomarker would be very useful to discriminate different forms of FSGS. Biomarkers have been searched both in blood and in urine samples. The search for plasma biomarkers has been basically focused on the permeabilizing factor. Research on the putative plasma factor began about two decades ago [81, 82], and although some candidates have been proposed [83, 84], it has not been firmly demonstrated that any of them causes idiopathic FSGS. Certainly, one of the most promising proposed circulating factors was soluble urokinase receptor (suPAR), which was found to be increased in the serum of FSGS patients [8]. In a previous work, Wei et al. [85] showed that the urokinase receptor could be involved in the FPE of podocytes via activation of the
sb3-integrin pathway in a urokinase plasminogen activator receptor (uPAR) knockout mouse model [85]. Therefore, they hypothesized that maybe the soluble uPAR (suPAR) could be the FSGS causal circulating factor. suPAR levels were measured in serum samples of 78 subjects with FSGS, 25 with MCD, 16 with MN, 7 with pre-eclampsia, and in 22 healthy individuals. Blood suPAR levels were higher in the FSGS patient group than in the rest of the studied groups and, moreover, suPAR levels were also higher in the FSGS patients that relapsed after kidney transplantation. In addition, the authors demonstrated that the uPAR recombinant form injected into a knockout mouse model induced proteinuria, reinforcing the idea that suPAR is the plasma circulating factor related to FSGS [8]. Unfortunately, later studies were unable to demonstrate the same results in independent cohorts [86–88]. Nor could it be firmly demonstrated that it was the cause of the disease [89, 90]. Moreover, plasma suPAR levels have also been found to be elevated in several extrarenal pathologies that can potentially be concomitant to FSGS, such as cancer or inflammatory disorders, among others [91–95]. Recent studies suggest that both urinary levels of suPAR [96, 97] and uPAR detection in kidney biopsies [98] may be useful in the diagnosis of primary FSGS, but further investigation is needed. Anti-CD40 blood levels have also been associated with FSGS, with 78% accuracy to predict post-transplant FSGS recurrence [99], although further studies are required to confirm these results. Recently, it has been shown that plasma of relapsing FSGS patients induces the expression of several specific genes upon cultured podocytes and the authors suggest that this could be used to distinguish FSGS recurrence from other types of renal disease. As an example, analysis of interleukin-1β gene expression induced by serum of recurrent FSGS patients shows >80% sensitivity and specificity to discriminate relapsing FSGS patients from other nephropathies [100]. Although the study was elegantly designed, it represents an indirect method on cultured podocytes, cells that need several days to differentiate (from 7 to 14 days) [101], hence it would not allow a fast diagnosis of FSGS relapse, making it difficult to use in current clinical practice. Finally, plasma miRNAs have also been explored as potential biomarkers to detect primary FSGS and several of these have been associated to the disease [102–104].

Urine has also been exploited as a biomarker source. In 2007, Varghese et al. [105] performed two-dimensional electrophoresis (2DE) of urine samples from several groups of patients (FSGS, IgAN, MGN, and diabetic nephropathy) with the aim of finding biomarkers to distinguish glomerulopathies. They quantified the relative abundance of each spot (that represents a protein) and, based on these data, they designed a prediction algorithm. Although this study was not focused on FSGS, it revealed that variations in the urinary proteome could be useful to discriminate kidney diseases with proteinuria. Similarly, in a rat model of induced FSGS, a serial analysis of urine samples using 2DE revealed that the proteomic profile changed along the course of

FIGURE 1: Milestones for primary FSGS biomarker identification. Timeline of research studies focused on finding putative biomarkers to detect primary FSGS in blood, kidney tissue and urine.
the disease and that some proteins appeared before the sclerotic lesions, suggesting that they could be useful as early biomarkers [106]. To our knowledge, the first and only urinary biomarker that has been specifically associated with post-transplantation recurrent FSGS is apolipoprotein A-Ib (apoA-Ib), a modified form of apoA-I, described by Lopez-Hellín et al. in 2013 [107]. Results from two cohorts [10, 107] have shown that the presence of this form in urine allows the detection of recurrent FSGS patients with high specificity and sensitivity (>87% and >90%, respectively). ApoA-Ib also has a potential prognostic value, as it can be found in urine before the FSGS recurrence episodes [10]. Although the exact role of apoA-Ib in FSGS is unknown, other authors have also found increased levels of apoA-I [108] or the presence of high molecular weight forms of apoA-I [109] in urine of FSGS patients, reinforcing the idea that either apoA-I or the mechanisms that modify this lipoprotein are involved in the pathogenic mechanism of this disease [110]. The potential role of this biomarker to discriminate primary FSGS in native kidney is currently being pursued, but preliminary results obtained with idiopathic FSGS patients before kidney transplantation pointed out that the detection of apoA-Ib in native kidney patients is associated with a worse prognosis [10]. Regarding urinary mRNAs, several of them can be found differentially in urine of primary FSGS patients [111, 112], but their potential as biomarkers remains to be studied.

CONCLUSIONS

As reviewed in this work, the diagnosis and management of primary FSGS is not a trivial issue, as knowledge of this pathology holds ‘several types of truths’ [113], as every matter of study. Management of this rare disease with an unknown aetiology is based on empirical knowledge related to the response of primary FSGS to different treatments, which is per se extremely difficult. Experimental studies have provided fundamental data to better understand the disease and it is expected that the new biomarkers will allow an improved diagnostic algorithm for primary FSGS.

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