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Review

eGFR, cystatin C and creatinine in shrunken pore syndrome

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ABSTRACT

Shrunken pore syndrome (SPS) is a condition in which the estimated glomerular filtration rate (eGFR) based on serum/plasma cystatin C concentration is significantly lower than the eGFR based on creatinine. According to the literatures, the diagnosis of SPS could be defined when the $eGFR_{cystatin\ C}$ is < 70% of $eGFR_{creatinine}$. Although the incidence of SPS varies in different patient populations and healthy seniors, it has been demonstrated that patients with SPS have poor prognosis. The present review has summarized its diagnosis, epidemiology, prognosis and possible pathophysiology basis. Moreover, we discuss the prevention and treatment of SPS in clinical practice as future challenges.

1. Introduction

The concept of "shrunken pore syndrome (SPS)" was first defined by Grubb et al. [1]. They observed consecutive plasma samples collected from 1349 patients, between 3 and 95 years old, and determined the plasma levels of cystatin C, β2-microglobulin, beta-trace protein (BTP), retinol-binding protein (RBP), and creatinine. The patients were divided into three groups according to different estimated glomerular filtration rates (eGFR) based on cystatin C and creatinine. The ratios of cystatin C/creatinine, β2-microglobulin/creatinine, and BTP/creatinine were significantly higher in patients when $eGFR_{cystatin\ C}$ was less or equal to 60% of $eGFR_{creatinine}$. The molecular weights of β2-microglobulin (molecular mass 11,600 Da), BTP (molecular mass 23,000 Da) and RBP (molecular mass 21,000 Da) are similar to that of cystatin C (molecular mass 13,000 Da), which is much higher than that of creatinine (molecular mass 113 Da), but the production of these proteins is not regulated by a similar mechanism. The probable explanation for the simultaneous increase of creatinine ratios in patients with $eGFR_{cystatin\ C}$ < 60% of $eGFR_{creatinine}$ is that their elimination by the kidneys is decreased.

GFR is used to assess the kidney filtering capacity and renal function. Normal kidney filtering capacity relies on the function and structural integrity of the glomerular filtration barrier. The glomerular filtration barrier between the vasculature and the urinary space consists of three layers: the fenestrated endothelial cells (ECs), the podocytes, and the intervening glomerular basement membrane [2]. Defects in any one of the three layers may cause proteinuria, kidney failure, and eventual end-stage renal disease [3–5]. Normally, a remarkably small fraction of albumin and other large plasma proteins pass across the glomerular capillary wall despite the massive filtration of water and small solutes. Glomerular EC fenestrae are essential for the clearance of low molecular weight products from circulation by filtration [6]. Glomerular EC fenestrae are plasma membrane lining transcellular pores ranging from 70 to 100 nm in diameter, can be observed by transmission and scanning electron microscopy [7]. Grubb et al. [1] suggested that the concurrent increase of plasma levels of small molecule like cystatin C, β2-microglobulin, BTP, and RBP in patients with $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio < 0.60 is due to a reduction in pore diameter of the glomerular filtration barrier, and they proposed the designation "SPS" for this pathophysiological state. The shrunken size and density of glomerular EC fenestrae may be the cause of the reduction in pore diameter of the glomerular filtration barrier for SPS.

2. Definition

The concept of SPS was derived from the pathophysiologic state in patients whose eGFR was evaluated based on cystatin C (CAPA equation) and creatinine (LM_{rev} equation) (according to www.egfr.se). When the $eGFR_{cystatin\ C}$ is < 70% of $eGFR_{creatinine}$, *i.e.,* the $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio is < 0.70, and no non-renal factors influence the estimates, the patient suffers from SPS with a strong increase in morbidity and mortality, *inter alia* due to cardiovascular manifestations

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[8–12]. However, varying clinical settings need different $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$ ratio cut-off levels. The increase in morbidity and mortality is inversely proportional to the $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$ ratio starting at a ratio of 0.85 using the equation pair CAPA/LM_{rev} in cardiac surgery patients [12]. It should be emphasized that it has not yet been established that the SPS exists in children younger than 18 years [13].

3. Incidence and prognosis

The incidence of SPS varies from 2.1% to 22.1% in different patient populations [9,12,14,15] and 0.7% in healthy seniors [10]. This wide range in the reported incidence of SPS has been influenced by the patient population studied and by using different equation pairs. As SPS was identified recently, limited studies of its clinical consequences have been conducted. An early investigation showed that long-term mortality in patients undergoing elective coronary artery bypass grafting is higher in patients suffering from SPS than in patients without the syndrome, whether the preoperative GFR was normal or reduced [9]. Preoperative presence of SPS defined by the equation pair CAPA and LM_{rev} with a cut-off of 70% independently predicts poorer survival (HR 2.941; 95% CI, 1.842–4.694; $p < 0.001$) in this patient population [9]. In addition, SPS had a predictive value of overall morbidity and mortality in healthy seniors [10]. The Kaplan-Meier survival analysis for healthy seniors exhibiting SPS defined at 60%, 70%, and 80% $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$ showed significantly lower survival in participants with SPS, and the survival differences become larger when the cut-off for the definition of SPS is decreased [10]. Moreover, heart failure patients with SPS had a significantly 3.5-fold increased risk of having right ventricular systolic dysfunction compared with patients without SPS [14]. Similarly, 1- and 3-year mortality (26% & 51%) for patients undergoing elective cardiac surgery suffering from SPS at the cut-off ratio of 0.7–0.8 increased significantly compared with the patients without SPS [12]. The shrinking of the glomerular pores also occurs in pregnant women and is particularly pronounced in cases of preeclampsia (PE). It has been reported that women with SPS at the first trimester have a high risk of PE during pregnancy [15]. $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$ ratio was inversely associated with PE (OR 0.98, 95% CI [0.96,0.99]; $p = .04$) independent of kidney function [15]. Table 1 summarizes all studies associating SPS. Whether SPS is associated with an increased risk for renal endpoints, including proteinuria or progression to kidney failure, is still unclear. Further studies in different clinical settings are required.

4. Possible pathophysiologic basis of SPS

The decrease of the $eGFR_{cystatin\ C}$/$eGFR_{creatinine}$ ratio is due to an increase of cystatin C and/or a decrease of creatinine levels. Cystatin C, encoded by *CST3*, is an inhibitor of cysteine [16] and is expressed in all nucleated cells [17]. The production of cystatin C is constant, and it is freely filtered through the glomeruli [18]. However, it cannot be used in calculations of 24 h urinary cystatin C clearance, because it is completely reabsorbed and metabolized by renal tubular epithelial cells [16,18]. The advantage of cystatin C as an eGFR-marker compared with creatinine is that it is less dependent on the body composition, such as muscle mass [19–22]. The serum levels of cystatin C are higher in individuals with morbid obesity [23], diabetes mellitus [24], and metabolic syndrome [25]. But beyond that, the change of blood cystatin C levels could indicate that glomerular filtration quality is altered, and the readout of blood cystatin C concentration might have different clinical implications [10,26]. The concurrent increase in plasma levels of β2-microglobulin, BTP, and RBP, which have molecular weights similar to cystatin C, in many patients with significantly lower $eGFR_{cystatin\ C}$ than $eGFR_{creatinine}$ suggests the presence of SPS. These proteins were selected because the production of cystatin C does not generally influence the production of these proteins *via* the same mechanism [1]. High cystatin C is obviously associated with

Table 1
Studies on shrunken pore syndrome.

Author	Year	Population	N	Estimating equation	Results
Purde	2015	Healthy seniors	1467	Cy: CAPA, CKD-EPI Cr: LM_{rev}, CKD-EPI	Participants with SPS show significantly lower survival.
Grubb	2015	Consecutive patients	1349	Cy: CAPA Cr: LM_{rev}	The ratios of cystatin C/creatinine, β2-microglobulin/creatinine, and BTP/creatinine are significantly higher in patients with SPS.
Dardashti	2015	Patients undergoing elective coronary artery bypass grafting	1638	Cy: CAPA, CKD-EPI Cr: LM_{rev}, CKD-EPI	SPS is found to be a significant predictor for mortality.
Christensson	2016	Heart failure patients	143	Cy: CAPA, CKD-EPI Cr: LM_{rev}, CKD-EPI	Heart failure patients with SPS are at increased risk of having right ventricular systolic dysfunction.
Leion	2017	Children	702	Cy: CAPA, Berg, CKD-EPI, FAS, Schwartz Cr: LM_{rev}, CG, CKD-EPI, MDRD, $Schwartz_{original}$, $Schwartz_{IDMS}$, Counahan-Barratt, Gao, FAS_{AGE}, FAS_{HEIGHT}	SPS has not been confirmed in children.
Risch	2017	Pregnant women	183	Cy: CKD-EPI, CAPA, FAS Cr: CKD-EPI, FAS, LM_{rev}	$eGFR_{CysC}$/$eGFR_{Crea}$ ratios in the first trimester are associated with later development of preeclampsia.
Herou	2019	Cardiac surgery patients	4719	Cy: CAPA, CKD-EPI Cr: LM_{rev}, CKD-EPI	Short- and midterm mortality increases markedly with an increasing degree of SPS.
Almén	2019	Swedish Caucasian patients above 18 years	156	Cy: CAPA Cr: LM_{rev}	All-cause mortality is higher in patients with SPS.
Campos	2019	Pregnant women	74	Cr: LM_{rev}, CKD-EPI, FAS	Arg/ADMA ratio is decreased in women with SPS.

cardiovascular disease (CVD) risk factors even without chronic kidney disease (CKD) [27–29]. This may partially explain why SPS is a strong predictor of incident CVD. A previous study suggested that cystatin C might inhibit the permeability of ECs [30]. The permeability of ECs is dependent on the fractional area of the fenestrae [31], and without fenestrae, the kidney could not perform its primary function of clearing low molecular weight products from circulation [6]. It is possible that the pathophysiology of SPS is related to the dysfunction of EC fenestrae. Besides the selected proteins, proteomic studies show that many plasma proteins change in SPS or with reduced GFR [11]. A survey of the literature suggests that of the 30 protein changes specific for SPS, 18 promote, or are associated with, atherosclerosis [11], such as monocyte chemotactic protein-3 [32], osteoprotegerin [33], interleukin-6 [34], and C-X-C motif chemokine 10 [35]. These retained substances are supposed to lead to increased overall mortality and disease-specific morbidity and mortality.

Serum creatinine is a very small molecule and is freely filtered across glomeruli [36]. It is the most widely used endogenous filtration marker [37]. However, the production of creatinine is not constant, since it is affected by body composition and diet. Dietary protein deficiency leads to a reduced level of creatinine [38,39]. In other conditions, diminished muscle mass (such as by cirrhosis) leads to decreased serum creatinine levels and overestimation of GFR [40]. Furthermore, secretion and reabsorption of creatinine by renal tubular epithelial cells and extrarenal clearance also influence serum creatinine levels [36,41]. The performance of creatinine-based equations is particularly poor in patients with CKD, so eGFR equations, including cystatin C alone or in combination with creatinine, are more reliable [42]. Of course, the best way to measure GFR is using exogenous substances such as inulin or iohexol, but this is costly and complex [43–46]. If the eGFR measurements obtained by cystatin C– or creatinine-based equations do not agree, *e.g.,* if the $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio is outside the interval of 0.8–1.20, a clinical evaluation of the patient must be performed, including of non-renal factors. If the ratio $eGFR_{cystatin\ C}/eGFR_{creatinine}$ is consistently ≤ 0.7 without other influencing factors, shrinking of the glomerular pores should be considered. As SPS is associated with poor outcomes, accurate $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio estimation is an important aspect of many clinical decisions. The CAPA equation based on cystatin C and the LM_{rev} equation based on creatinine are recommended for evaluating the existence of SPS after excluding non-renal factors.

It is well known that in women with PE, glomerular ECs are markedly thickened, and that the size and density of glomerular EC fenestrae are reduced compared to those in normal pregnancy [26]. This ultrastructural change is associated with a reduced GFR [47], and GFR recovers as the condition resolves and fenestrae reappear [48]. The SPS may be an early manifestation or compensatory change of kidney injury by EC swelling, further influence the proper size and density of fenestrae (Fig.1). Proteinuria, even kidney failure can occur with the injury aggravating.

In addition, the glomerular capillary wall is thought to function as both a size- and charge-selective barrier [49]. We assume that the change of glomerular filter quality may be not only related to the pore size but also the charge barrier. Molecules with different weights and charges can be employed to determine the real cause of the altered glomerular filtration barrier.

5. Prevention and treatment of SPS

No effective treatment has been achieved for SPS. The proper size and density of fenestrae are indispensable for the hydraulic conductivity of the glomerular capillary wall [50]. The promotion of EC fenestrae formation would be desirable to avoid kidney failure and may increase glomerular filtration of small molecules in SPS. A previous study demonstrated that loss of integrity of the EC glycocalyx layer results in decreased glomerular filtration barrier function [51]. The glycocalyx could serve as a new therapeutic target to restabilize glomerular filtration function [4]. In addition, recent research has found that the arginine (Arg)/asymmetric dimethylarginine ratio, as a marker of nitric oxide (NO) bioavailability, is decreased in women with SPS, who subsequently develop PE. Antagonized impairment of NO metabolism (*e.g.*, Arg treatment) may be a preventive measure to deal with SPS in pregnant women [15]. Furthermore, some proteins are specific for SPS that play a key role in the development of atherosclerosis. These might be potential targets for therapeutic interventions to reduce the risk of cardiovascular complications in patients with SPS [11].

6. Future challenges

Despite the importance of the new concept of SPS, it is increasingly recognized that the optimal cut-off levels and pathoanatomy must be researched to improve the definition of SPS and its application in predicting outcomes.

The cut-off of $eGFR_{cystatin\ C}$ being 70% of $eGFR_{creatinine}$, recommended as the definition of SPS, was chosen from eGFR ratios in patients undergoing elective coronary artery bypass grafting [9] and cardiac surgery [12], but is somewhat arbitrary and may not be the best for identifying risk in other patient populations. Varying clinical settings need different $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio cut-off levels. Obtaining suitable cut-off levels in different patient populations will require that the sample sizes be very large to determine the occurrence of clinical consequences at various levels. Further studies are thus needed to provide insight into the optimal cut-off levels in different patient populations.

Pathoanatomic changes can provide strong evidence of pathological processes in SPS. However, determining the pathoanatomy of SPS is challenging because of the limited availability of suitable *in vitro* and *in vivo* EC fenestrae models and the requirement for electron microscopy to image these sub-100-nm structures. The study of EC fenestrae is at a relatively early stage, and a number of questions remain to be resolved.

A more rigorous way to confirm SPS is to use invasive methods in which substances of different molecular sizes and charges that are only excreted by glomeruli are injected, and their plasma levels or urine clearance are determined. There are also a few studies in humans [52–55] in which these substances have been used to detect the presence of shrunken or widened glomerular pore sizes, but the required complex procedures and ethical issues will probably not allow their use in the general population.

Although the possible pathophysiologic basis of SPS might be the one discussed here, it still cannot directly explain the cause of increased mortality and morbidity related to SPS. Future challenges are to elucidate the etiology and pathophysiology of SPS and to find possible preventive and therapeutic interventions.

7. Conclusions

SPS is a new concept defined as the $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio being < 0.70, with no non-renal factors influencing the estimates. It predicts poor clinical outcomes in different patient populations. The shrunken size and density of glomerular EC fenestrae may contribute to SPS, resulting in decreased small molecule clearance. The recovery of the fenestrae may be a promising treatment for SPS.

Consent for publication

All the authors agree to publication of this review.

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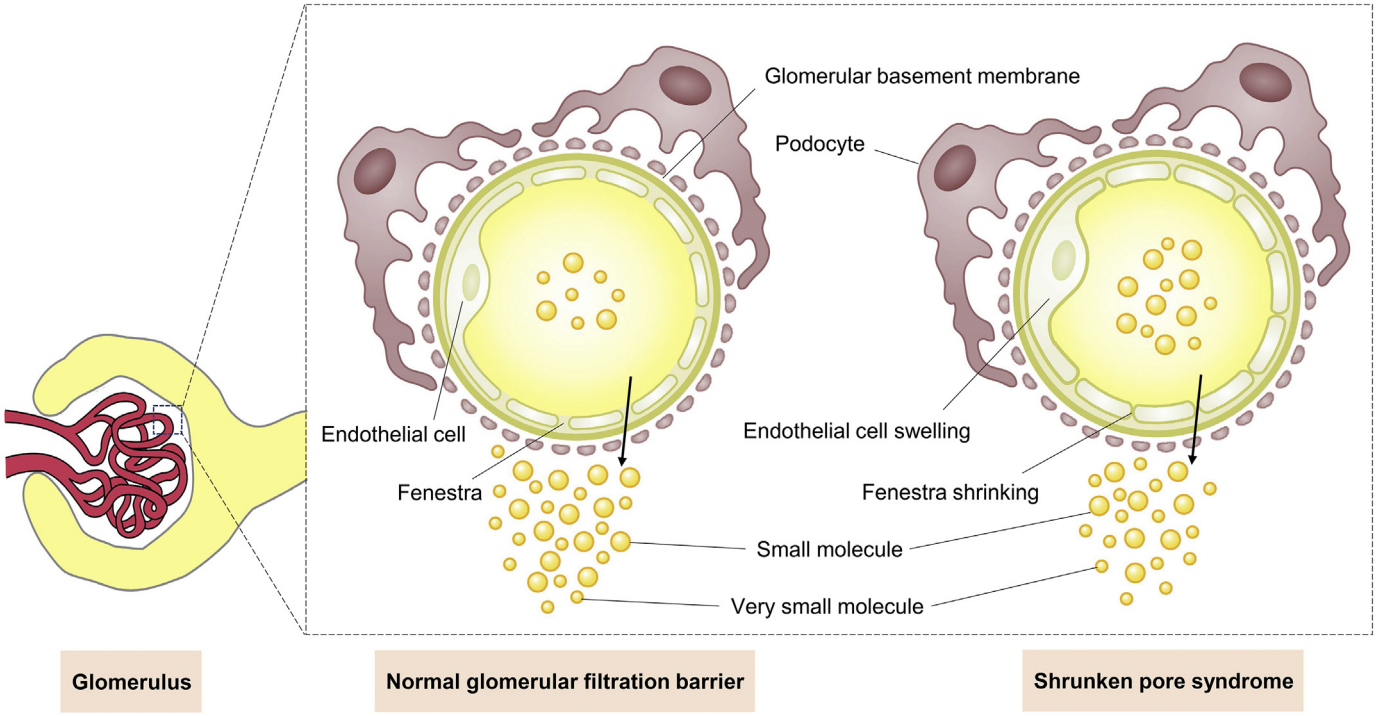

Fig. 1. Possible pathophysiology of shrunken pore syndrome.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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