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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

CLINICAL OVERVIEW

Glomerular filtration and shrunken pore syndrome in children and adults

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Abstract

A major function of the kidney is to, by glomerular filtration, maintain the overall steady-state of 5–30 kDa proteins, many of which are signalling molecules. This function of the kidney has been overlooked, since predominantly low-molecular-mass substances <1 kDa have been used to measure or estimate glomerular filtration rate (GFR). The use of cystatin C (13 kDa) as a marker of GFR has allowed the discovery that the filtration of 5–30 kDa molecules can be selectively impaired defining the shrunken pore syndrome. The discovery, pathophysiology, morbidity (mainly cardiovascular manifestations) and mortality of this syndrome are described.

KEYWORDS
creatinine, cystatin C, glomerular filtration rate, kidney, shrunken pore syndrome

1 | THE GLOMERULAR FILTRATION PROCESS

The production of primary urine is based upon ultrafiltration of blood plasma through a multi-layered complex membrane. The glomerular filtration rate (GFR) is the volume of primary urine produced during each time unit and it is usually expressed as millilitres per minute (ml/min) or ml/min/1.73 m^2 when it is standardised to a body surface area of 1.73 m^2. Approximately 95% of the glomerular filtrate is water (0.018 kilodaltons, kDa). Different models are used to describe the filtration process and the simplified functional-pore model is frequently used.[1] The filtration of molecules of different sizes is characterised by their sieving coefficient, which is the ratio of their concentration in primary urine and in plasma.[2] For small molecules <1 kDa, the sieving coefficients are 1 and such small molecules are generally used for estimation or determination of GFR provided they do not undergo tubular reabsorption or secretion. Such molecules are, for example, creatinine (0.11 kDa), ^{51}Cr-EDTA (0.34 Da), iohexol (0.82 kDa), ^{125}I-iothalamate (0.64 kDa).[2-4] The sieving coefficients for molecules bigger than 5 kDa is <1 and is progressively reduced with increasing size.[2] But for molecules around 30 kDa the sieving coefficient is still about 0.09 and, due to the high production of primary urine (around 140 L/1.73 m^2 per day) in healthy persons, this means that most molecules up to 30 kDa are predominantly eliminated by glomerular filtration.[2,5,6] Proteins below 30 kDa correspond to about 36% of the total human proteome[6] and comprise a large number of proteins with important signalling functions.[7]

2 | DETERMINATION AND ESTIMATION OF GFR

Determining GFR is an invasive process that involves intravenous injection of an exact amount of a low-molecular-weight substance eliminated solely by glomerular filtration and with no tubular reabsorption or secretion and measuring the disappearance of the substance from blood or its excretion in urine.[3,4] The presently most used such substance is iohexol (0.82 kDa), which is non-radioactive

Abbreviations: CAPA equation, Caucasian-Asian-Paediatric-Adult equation; $eGFR_{creatinine}$, creatinine-based estimate of glomerular filtration rate; $eGFR_{cystatin\ C}$, cystatin C-based estimate of glomerular filtration rate; GFR, glomerular filtration rate; kDa, kilodalton; SPS, shrunken pore syndrome.

and, therefore, particularly suitable for use in children and fertile women.[3,4,8] However, determination of iohexol clearance is time-consuming and expensive and might be technically problematic, especially in small children. GFR estimating equations are, therefore, generally used in clinical practise and these are based upon the plasma levels of creatinine or cystatin C. Plasma creatinine is strongly associated with the muscle mass of an individual and the strong changes in muscle mass during childhood generally requires distinct creatinine-based GFR estimating equations for children and adults. For example, the Schwartz$_{creatinine}$ equation is often used for children and the CKD-EPI$_{creatinine}$ equation for adults.[9,10] However, progress in the development of creatinine-based GFR estimation equations have allowed the construction of equations, for example, LMR18 and EKFC, valid for both children and adults.[11,12] Plasma cystatin C is, in contrast to plasma creatinine, not associated with the muscle mass of an individual and the same cystatin C-based GFR estimating equation can therefore be used both for children and adults.[13-15] For example, the Caucasian-Asian-Paediatric-Adult (CAPA) equation works for all individuals above one year of age and does not, in contrast to creatinine-based equations, require terms for sex and 'race' to compensate for differences in muscle mass between individuals.[15]

Improved diagnostic performance of GFR estimating equations were developed by the use of complex equations containing both cystatin C and creatinine and this was true both for children[16] and adults.[17] However, it turned out that using the arithmetic mean of the results of a cystatin C-based GFR estimating equation (eGFR$_{cystatin\ C}$) and a creatinine-based estimating equation (eGFR$_{creatinine}$) performed as well as, or even better,[18-20] than complex equations with both cystatin C and creatinine terms. This was initially shown for adults,[18,19] but was later found true also for children.[20-24]

3 | OPTIMAL USE OF GFR ESTIMATING EQUATIONS

The observation that use of the arithmetic mean of eGFR$_{cystatin\ C}$ and eGFR$_{creatinine}$ is the best way of estimating GFR, with 90–91% of the results within ±30% of GFR measured by invasive gold standard methods, has allowed the development of an efficient way of estimating GFR in the clinical routine valid for both children and adults.[20] If eGFR$_{cystatin\ C}$ and eGFR$_{creatinine}$ agree, within for example 20%, the average (eGFR$_{cystatin\ C}$ + eGFR$_{creatinine}$)/2 is a reliable estimate of GFR and no invasive determination of GFR is required.[20] For some paediatric populations the average of eGFR$_{cystatin\ C}$ + eGFR$_{creatinine}$ is a reliable estimate of GFR even when the estimates differ by up to 40%.[23] The closer the agreement between eGFR$_{cystatin\ C}$ and eGFR$_{creatinine}$, the more reliable is the average value as a GFR estimate. If eGFR$_{cystatin\ C}$ and eGFR$_{creatinine}$ do not agree, a clinical evaluation of the patient has to be performed, assessing the presence of non-renal factors influencing eGFR$_{cystatin\ C}$ or eGFR$_{creatinine}$. If such a factor can be found for one of the estimates, the other, uninfluenced, estimate is used as the best GFR estimate. The most common such factors are abnormally low muscle mass, resulting in low creatinine levels and high eGFR$_{creatinine}$ and treatment with high doses of glucocorticoids resulting in high cystatin C levels and low eGFR$_{cystatin\ C}$.[20] Tools for these calculations are present in several laboratory information management systems and on the internet (http://egfr.se/eGFRen.html).

4 | SHRUNKEN PORE SYNDROME IN ADULTS AND CHILDREN: CLINICAL CONSEQUENCES

As stated above, if eGFR$_{cystatin\ C}$ and eGFR$_{creatinine}$ do not agree at an estimation of GFR, a clinical evaluation of the patient has to be performed to search for the presence of non-renal factors influencing eGFR$_{cystatin\ C}$ or eGFR$_{creatinine}$. In 2015 it was observed that if no such factors could be found and eGFR$_{cystatin\ C}$ was less than 60 or 70% of eGFR$_{creatinine}$ in adult patients, they will suffer from a strong increase in long-term mortality and morbidity.[25-28] As the original study indicated that a selective decrease in the renal filtration of 5–30 kDa molecules occurred in these patients despite an unaffected filtration of low-molecular-mass molecules, like creatinine and water, the syndrome was designated shrunken pore syndrome (SPS).[25] It should be observed that the definition of SPS as an eGFR$_{cystatin\ C}$/eGFR$_{creatinine}$-ratio <0.60 or 0.70 is valid for all three pairs of cystatin C- and creatinine-based GFR estimating equations so far tested.[6,28] These pairs are CAPA$_{cystatin\ C}$ - LMR$_{creatinine}$, CKD-EPI$_{cystatin\ C}$ - CKD-EPI$_{creatinine}$ and FAS$_{cystatin\ C}$ – FAS$_{creatinine}$.[6,7,25,26,28] Recent studies indicate that SPS is present also in children.[29,30] All epidemiologic studies in adults show that both morbidity and mortality is strongly increased in patients with SPS.[6,7,26-28] A study of 2871 adults with measured GFR and a median observation period of 5.6 years was published in 2020.[28] It demonstrated that the hazard ratio (HR) for death was 3.3 (95%CI: 2.5–4.5) for patients with SPS (defined by an eGFR$_{cystatin\ C}$/eGFR$_{creatinine}$-ratio <0.6), which was significantly higher than HR for death caused by cancer, cardiovascular disorders (CVD), diabetes or traditionally defined chronic kidney disease.[28] The prevalence of SPS in the total cohort was 11%.[28] In the sub-cohort of 567 individuals with normal measured GFR, no albuminuria and no prior diagnosis, the prevalence of SPS was still 5% and connected to a high HR for death of 14.[28] The specific death causes for patients with SPS were cardiovascular disease, chronic kidney disease, cancer and diabetes.[28] The prevalence of SPS in various adult populations has varied from 0.2 to 19%.[6] Few studies of SPS in children have been published[29,30] and in these populations, no increase in mortality has been noted during the relatively short observation periods although the prevalence in one study was 5%.[30] It should be observed that at this stage of our knowledge, there remains uncertainty about the magnitude of the associations between SPS in childhood or adolescence and cardiovascular morbidity and mortality in adulthood. Hard CVD outcomes, such as death, myocardial infarction or stroke are very unusual events in childhood or adolescence. Elevated blood pressure in childhood

or adolescence has been consistently associated with intermediate markers of CVD (for example, high pulse wave velocity, high carotid intima-media thickness, and left ventricular hypertrophy), but not with hard CVD outcomes. There is, however, some evidence of associations between childhood hypertension and hard CVD events in adulthood.[31-33] If SPS identified in childhood might contribute to an increased risk of CVD in adulthood is so far just a provocative hypothesis that needs to be tested.

5 | DIAGNOSTIC CONSIDERATIONS

As reported above, a diagnosis of SPS requires knowledge of the $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio. However, many healthcare providers supply either only $eGFR_{creatinine}$ or only $eGFR_{cystatin\ C}$. If in such a situation, $eGFR_{creatinine}$ is unexpectedly high or $eGFR_{cystatin\ C}$ unexpectedly low, SPS might be suspected. To reject or confirm this diagnosis the other type of GFR estimation has to be done so that the $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio can be determined.[6,25] No determination of GFR is required for a diagnosis of SPS since SPS occurs both with normal or reduced GFR.[6,25,26,28]

6 | THE PATHOPHYSIOLOGY OF SPS: HYPOTHETICAL TREATMENT OPTIONS.

About a decade before SPS was defined, studies of 5–30 kDa proteins and small molecules <1 kDa, like creatinine and urate, in pregnant females, demonstrated that a selective decrease in the glomerular elimination of 5–30 kDa proteins occurred in the last trimester of all pregnancies.[34] The selective decrease in the glomerular elimination of 5–30 kDa proteins in pregnancy is similar to that later described as characteristic for SPS.[6,7,25] The decrease in the elimination of 5–30 kDa proteins was significantly greater in pre-eclampsia than in normal pregnancy and the increase in plasma levels of 5–30 kDa proteins could therefore be used to diagnose this condition and also for optimal timing of delivery in patients with pre-eclampsia.[35] A few weeks after delivery the elimination of 5–30 kDa proteins returned to normal, with normal plasma levels of such proteins, indicating that the pathophysiological process of SPS is reversible.[6,35] Even before SPS was defined, it was known that raised levels of cystatin C and other 10–30 kDa proteins, like beta-2-microglobulin and beta-trace protein, were more strongly correlated to morbidity and mortality than raised levels of creatinine, although no consistent pathophysiological background to these observations could be offered.[36-41] Sarcopenia, with low production of creatinine and, therefore, increased levels of $eGFR_{creatinine}$, is strongly associated with morbidity and mortality and it has, therefore, been suggested that the high morbidity and mortality of SPS is connected to sarcopenia. However, this was carefully studied by Åkesson et al, who demonstrated that patient cohorts with SPS displayed higher mortality and morbidity compared to cohorts without SPS without significant differences in weight, body mass index, lean body mass index or $eGFR_{creatinine}$.[28]

Since about 36% of the proteins in the human proteome are predominantly eliminated by glomerular filtration,[6] a study of the proteomes in patients with or without SPS and with normal or reduced GFR was undertaken in an effort to elucidate the pathophysiology of SPS.[6,7] In this study, the plasma levels of 177 proteins in 156 patients with measured GFR were determined.[7] In a parallel study, the impact of the glomerular filtration rate on the human plasma proteome was investigated by determination of the levels of 2893 proteins in 389 patients with measured GFR.[42] The plasma levels of 678 proteins of the 2893 studied were found to increase in patients with reduced GFR and cystatin C displayed the highest correlation with measured GFR.[42] Patients with SPS displayed a proteome specific for SPS, independent of the GFR level, with raised levels of many 5–30 kDa proteins.[7] Among these proteins, several have previously been shown to carry signalling functions promoting the development of atherosclerosis,[7] which might explain the increase in cardiovascular morbidity and mortality associated with SPS. [6,7,26-28] A recent study on SPS and heart failure also showed the accumulation in SPS of proteins promoting development of atherosclerosis.[43] Examples of such proteins are osteoprotegerin, interleukin-6 and interleukin-18, and Table 1 displays all presently known SPS-specific proteins promoting development

TABLE 1 Shrunken pore syndrome specific proteins promoting, or being associated with, development of atherosclerosis

Abbreviation	Full protein name
MCP–3	Monocyte chemotactic protein–3
OPG	Osteoprotegerin
IL–1ra	Interleukin–1 receptor antagonist protein
IL2RA	Interleukin–2 receptor subunit alpha
IL–6	Interleukin–6
IL–17C	Interleukin–17C
IL–18	Interleukin–18
IL–18R1	Interleukin–18 receptor 1
TNF-R1	Tumour necrosis factor receptor 1
TNF-R2	Tumour necrosis factor receptor 2
MCP–1	Monocyte chemoattractant protein–1
CXCL11	C-X-C motif chemokine 11
CCL19	C-C motif chemokine 19
PD-L1	Programmed cell death 1 ligand 1
HGF	Hepatocyte growth factor
PTX3	Pentraxin 3
CXCL10	C-X-C motif chemokine 10
CTSL1	Cathepsin L1
CCL20	C-C motif chemokine 20
AXL	Tyrosine-protein kinase receptor UFO
4E-BP1	Eukaryotic translation initiation factor 4E-binding protein 1
ADAM-TS13	A disintegrin and metalloproteinase with thrombospondin motifs 13
CD163	Scavenger receptor cysteine-rich type 1 protein M130

Note: From Ref. [7] and.[43]

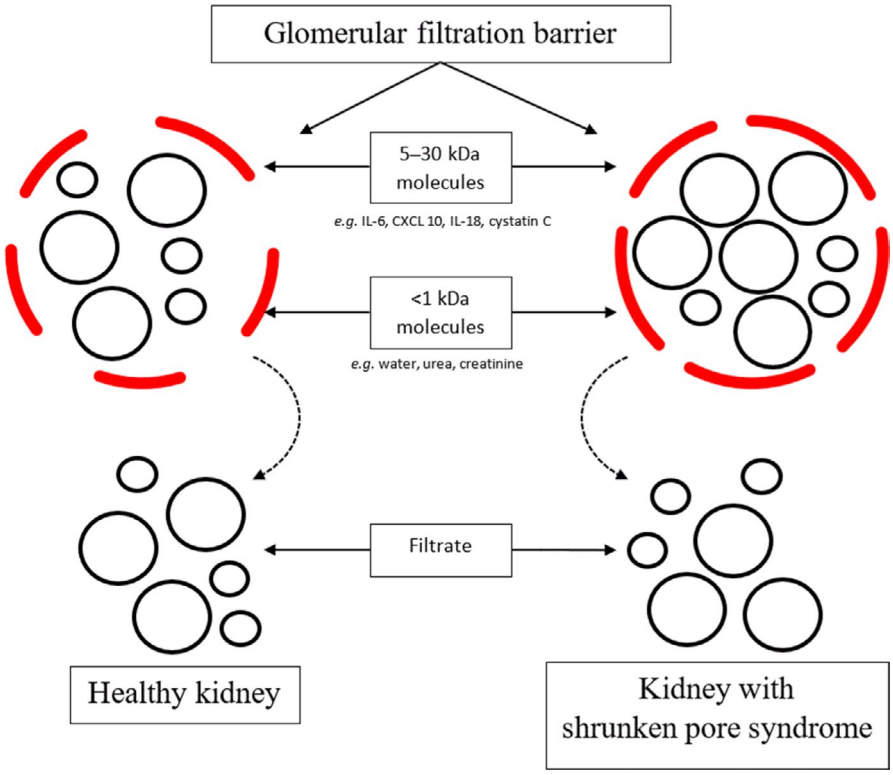

FIGURE 1 A pathophysiological model of shrunken pore syndrome, based upon the simplified functional pore model for the filtration process,[1] which does not specifically concern any of the three major components (endothelium, basement membrane, podocyte foot processes) of the complex glomerular filtration barrier.[44] A selectively reduced filtration of 5–30 kDa molecules, for example cystatin C, through the glomerular filtration barrier with unaltered filtration of smaller molecules results in the accumulation of 5–30 kDa proteins. These include signal proteins with detrimental effects, for example, promoting development of atherosclerosis. Some experimentally verified such proteins are interleukins 6 and 18 (IL-6, IL-18) and C-X-C motif chemokine 10 (CXCL 10). Recent data suggest that a thickening of the glomerular basement membrane results in SPS[45]

of, or being associated with, atherosclerosis.[7,43] A pivotal part of the pathophysiological process in SPS thus seems to be the accumulation of a large number of 5–30 kDa signalling proteins causing aberrations in several signalling pathways promoting the development of common disorders like cardiovascular disease, cancer and diabetes. Figure 1 displays this type of pathophysiological process.

The proposed pathophysiological process in SPS suggests different hypothetical treatment options. One would be the transplantation of a kidney without SPS. A second option would be to reduce the high levels of the most detrimental disease-promoting signal proteins by use of, for example, monoclonal antibodies analogously to the use of monoclonal antibodies in inflammatory disorders. A third one would be to develop haemodialysis procedures with sieving coefficients for 5–30 kDa similar to those of healthy kidneys. However, much more knowledge about SPS is required before any treatment option can be initiated.

7 | CONCLUSION

SPS is characterised by a selective decrease in elimination by glomerular filtration of 5–30 kDa proteins compared with elimination of substances <1 kDa. It can be diagnosed by comparing $eGFR_{cystatin\ C}$ with $eGFR_{creatinine}$. The syndrome is present if the $eGFR_{cystatin\ C}/eGFR_{creatinine}$-ratio <0.60 or 0.70 in the absence of non-renal factors influencing $eGFR_{cystatin\ C}$ or $eGFR_{creatinine}$. SPS is common in several adult populations and associated with a strong increase in morbidity and mortality. SPS has been demonstrated in paediatric populations, but its prevalence in different paediatric populations and its association with symptoms and clinical signs in childhood have not been investigated and such studies are therefore urgent challenges.

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Figure 1 was produced by Gabriel Grubb.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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