Glomerular filtration and shrunken pore syndrome in children and adults

Anders Grubb

Department of Clinical Chemistry, University Hospital, Lund, Sweden

Correspondence
Anders Grubb, Department of Clinical Chemistry, University Hospital, S-221 85 Lund, Sweden. Email: anders.grubb@med.lu.se

Funding information
This work was supported by Alfred Österlund’s Stiftelse

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 m² when it is standardised to a body surface area of 1.73 m². 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. 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. 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), 51Cr-EDTA (0.34 Da), iohexol (0.82 kDa), 125I-iothalamate (0.64 kDa). The sieving coefficients for molecules bigger than 5 kDa is <1 and is progressively reduced with increasing size. 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 m² per day) in healthy persons, this means that most molecules up to 30 kDa are predominantly eliminated by glomerular filtration. Proteins below 30 kDa correspond to about 36% of the total human proteome and comprise a large number of proteins with important signalling functions.

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. The presently most used such substance is iohexol (0.82 kDa), which is non-radioactive.

Abbreviations: CAPA equation, Caucasian-Asian-Paediatric-Adult equation; eGFRcreatinine, creatinine-based estimate of glomerular filtration rate; eGFRcystatin 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.3,4,2 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 children16 and adults.17 However, it turned out that using the arithmetic mean of the results of a cystatin C-based GFR estimating equation (eGFRcystatin C) and a creatinine-based estimating equation (eGFRcreatinine) 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 eGFRcystatin C and eGFRcreatinine is the best way of estimating GFR, with 90–91% of the results within ±10% 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 eGFRcystatin C and eGFRcreatinine agree, within for example 20%, the average (eGFRcystatin C + eGFRcreatinine)/2 is a reliable estimate of GFR and no invasive determination of GFR is required.20 For some paediatric populations the average of eGFRcystatin C + eGFRcreatinine is a reliable estimate of GFR even when the estimates differ by up to 40%.23 The closer the agreement between eGFRcystatin C and eGFRcreatinine, the more reliable is the average value as a GFR estimate. If eGFRcystatin C and eGFRcreatinine do not agree, a clinical evaluation of the patient has to be performed, assessing the presence of non-renal factors influencing eGFRcystatin C or eGFRcreatinine. 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 eGFRcreatinine and treatment with high doses of glucocorticoids resulting in high cystatin C levels and low eGFRcystatin 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 eGFRcystatin C and eGFRcreatinine 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 eGFRcystatin C or eGFRcreatinine. In 2015 it was observed that if no such factors could be found and eGFRcystatin C was less than 60 or 70% of eGFRcreatinine 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 eGFRcystatin C/eGFRcreatinine-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, LMRcreatinine, CKD-EPI creatinine, FAS cystatin C and 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.6,7,25–28 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 eGFRcystatin C/eGFRcreatinine-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 published29,30 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.\textsuperscript{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.

\section*{5 | DIAGNOSTIC CONSIDERATIONS}

As reported above, a diagnosis of SPS requires knowledge of the eGFR\textsubscript{cystatin C}/eGFR\textsubscript{creatinine} ratio. However, many healthcare providers supply either only eGFR\textsubscript{creatinine} or only eGFR\textsubscript{cystatin C}. If in such a situation, eGFR\textsubscript{creatinine} is unexpectedly high or eGFR\textsubscript{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\textsubscript{cystatin C}/eGFR\textsubscript{creatinine} ratio can be determined.\textsuperscript{6,25} No determination of GFR is required for a diagnosis of SPS since SPS occurs both with normal or reduced GFR.\textsuperscript{6,25,26,28}

\section*{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{36-41} Sarcopenia, with low production of creatinine and, therefore, increased levels of eGFR\textsubscript{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\textsubscript{creatinine}.\textsuperscript{28}

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

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Abbreviation & Full protein name \\
\hline
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 \\
\hline
\end{tabular}
\caption{Shrunken pore syndrome specific proteins promoting, or being associated with, development of atherosclerosis}
\end{table}

\textit{Note:} From Ref. [7] and.[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.

**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 $eGFR_{\text{cystatin C}}$ with $eGFR_{\text{creatinine}}$. The syndrome is present if the $eGFR_{\text{cystatin C}}/eGFR_{\text{creatinine}}$-ratio <0.60 or 0.70 in the absence of non-renal factors influencing $eGFR_{\text{cystatin C}}$ or $eGFR_{\text{creatinine}}$. 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.

**ACKNOWLEDGEMENTS**

Figure 1 was produced by Gabriel Grubb.

**CONFLICT OF INTEREST**

The author has no conflicts of interest to declare.

**REFERENCES**

1. Rippe B, Haraldsson B. Transport of macromolecules across microvascular walls: the two-pore theory. Physiol Rev. 1994;74:163-219.
2. Norden AGW, Lapsley M, Lee PJ, et al. Glomerular protein sieving and implications for renal failure in Fanconi syndrome. Kidney Inter. 2003;60:1885-1892.
3. Soveri I, Berg U, Björk J, et al. Measuring GFR: A systematic review. Am J Kidney Dis. 2014;64:411-424.
4. SBU. Skattning av njurfunktion. En systematisk litteraturöversikt. (Estimating kidney function. A literature survey) Stockholm: Statens beredning för medicinsk utvärdering (SBU); 2012. SBU-rapport nr 214. ISBN 978-91-85413-53-9. http://www.sbu.se/upload/Publikationer/Content0/1/Njurfunktion/Njurfunktion.pdf

5. Tenstad O, Roald AB, Grubb A, Aukland K. Renal handling of radio-labelled human cystatin C in the rat. Scand J Clin Lab Invest. 1996;56:409-414.

6. Grubb A. Shrunken pore syndrome – a common kidney disorder with high mortality. Diagnosis, prevalence, pathophysiology and treatment options. Clin Biochem. 2020;83:12-20.

7. Sällman-Almén M, Björk J, Nyman U, et al. Shrunken pore syndrome is associated with increased levels of atherosclerosis-promoting proteins. Kidney Int Rep. 2019;4:67-79.

8. Delaney P, Melsom T, Ebert N, et al. Iohexol plasma clearance

9. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple es

10. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular fil -

11. Björk J, Nyman U, Delaney P, et al. A novel method for creati

12. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple esti

13. Bökenkamp A, Domanetzki M, Zinck R, Schuman G, Byrd D, B

14. Bouvet Y, Bouissou F, Coulais Y, et al. GFR is better estimated by

15. Grubb A, Horio M, Hansson LO, et al. Generation of a new Cys
tin C-based estimating equation applicable in children. Scand J Clin Lab Invest. 2020;80:456-463.

16. Pottel H, Björk J, Courbebaisse M, et al. Development and vali

dation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. Ann Intern Med. 2021;174:183-191.

17. Bökenkamp A, Domanetzki M, Zinck R, Schuman G, Byrd D, Broddehl J. Cystatin C – a new marker of glomerular filtration rate in children independent of age and height. Pediatrics. 1998;101:875-881.

18. Bökenkamp A, Domanetzki M, Zinck R, Schuman G, Broddehl J. Reference values for cystatin C serum concentrations in children. Pediatr Nephrol. 1998;12:125-129.

19. Grubb A, Horio M, Hansson LO, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate using seven assays standardized to the international calibrator. Clin Chem. 2014;60:974-986.

20. Bouvet Y, Bouissou F, Coulais Y, et al. GFR is better estimated by considering both serum cystatin C and creatinine levels. Pediatr Nephrol. 2006;21:1299-1306.

21. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008;51:395-406.

22. Nyman U, Grubb A, Sterner G, Björk J. Different equations to com
bine creatinine and cystatin C to predict GFR. Arithmetic mean of existing equations performs as well as complex equations. Scand J Clin Lab Invest. 2009;69:619-627.

23. Grubb A, Nyman U, Björk J. Improved estimation of glomerular fil
tration rate (GFR) by comparison of eGFR_cystatin C and eGFR_creatinine. Scand J Clin Lab Invest. 2012;72:73-77.

24. Grubb A. Non-invasive estimation of glomerular filtration rate (GFR). The Lund model: simultaneous use of cystatin C- and creatinine-based GFR-prediction equations, clinical data and an in
ternal quality check. Scand J Clin Lab Invest. 2010;70:65-70.

25. den Bakker E, Gemke R, van Wijk JAE, et al. Accurate eGFR re
porting for children without anthropometric data. Clin Chim Acta. 2017;474:38-43.

26. Leion F, Hegbrant J, den Bakker E, et al. Estimating glomerular fil
tration rate (GFR) in children. The average between a cystatin C- and a creatinine-based equation improves estimation of GFR in both children and adults and enables diagnosing Shrunken Pore Syndrome. Scand J Clin Lab Invest. 2017;77:338-344.

27. den Bakker E, Gemke R, van Wijk JAE, Heubeck I, Stoffel-Wagner B, Bökenkamp A. Combining GFR estimates from cystatin C and creatinine—what is the optimal mix? Pediatr Nephrol. 2018;33:1553-1563.

28. den Bakker E, Gemke R, Bökenkamp A. Endogenous markers for kidney function in children: a review. Crit Rev Clin Lab Sci. 2018;55:163-183.

29. Grubb A, Lindström V, Jonsson M, et al. Reduction in glomerular pore size is not restricted to pregnant women. Evidence for a new syndrome: ‘Shrunken pore syndrome’. Scand J Clin Lab Invest. 2015;75:333-340.

30. Dardashti A, Nozohoor S, Grubb A, Bjursten H. Shrunken Pore Syndrome is associated with a sharp rise in mortality in patients undergoing elective coronary artery bypass grafting. Scand J Clin Lab Invest. 2016;76:74-81.

31. Purde MT, Nock S, Risch L, et al. The cystatin C/creatinine ratio, a marker of glomerular filtration quality: associated factors, refer
ence intervals, and prediction of morbidity and mortality in healthy seniors. Transl Res. 2016;169:80-90.

32. Åkesson A, Lindström V, Nyman U, et al. Shrunken pore syndrome and mortality: a cohort study of patients with measured GFR and known comorbidities. Scand J Clin Lab Invest. 2020;80:412-422.

33. den Bakker E, Heubeck I, Stoffel-Wagner B, van Wijk JAE, Gemke R, Bökenkamp A. The Shrunken Pore syndrome– also in the Kindersalter? Nieren- and Hochdruckkrankheiten. 2017;Jahrgang 46, Nr. 1:9–10. docplayer.org/40832815-issn-post-vertriebsstueck-entgelt-bezah lt-b-1185-e-dustri-verlag-dr-karl-feistle-bajuver-enring-4-d-deise nhofen-oberhaching.html

34. den Bakker E, Gemke RJ, van Wijk JA, Heubeck I, Stoffel-Wagner B, Bökenkamp A. Evidence for shrunken pore syndrome in children. Scand J Clin Lab Invest. 2020;80:32-38.

35. ESCAPE Trial Group, Wühl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. 2009;361:1639-1650.

36. Krmar RT, Ferraris JR. Clinical value of ambulatory blood pressure monitoring in pediatric patients after renal transplantation. Pediatr Nephrol. 2018;33:1327-1336.

37. Yang L, Magnussen CG, Yang L, Bovet P, Xi B. Elevated blood pressure in childhood or adolescence and cardiovascular outcomes in adulthood: A systematic review. Hypertension. 2020;75:948-955.

38. Kristensen K, Lindström V, Schmidt C, et al. Temporal changes of the plasma levels of cystatin C, beta-trace protein, beta-2-microglobulin, urate and creatinine during pregnancy indicate continuous alterations in the renal filtration process. Scand J Clin Lab Invest. 2007;67:612-618.

39. Damm D, Pariza P, Grubb A, Stevens H. Predicting maternal morbidity in hypertension in pregnancy with the “shrunken pore syndrome” ratio for optimal timing of delivery. Pregnancy Hypertension. 2018;13(suppl. 1):108-109.

40. Jernberg T, Lindahl B, James S, et al. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. Circulation. 2004;110:2342-2348.

41. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2005;352:2049-2060.

42. Bökenkamp A. Herget-Rosenthal, Bökenkamp R. Pediatr Nephrol. 2006;21:1223-1230.

43. Shafi T, Parekh RS, Jaar BG, et al. Serum β-trace protein and risk of mortality in incident hemodialysis patients. Clin J Am Soc Nephrol. 2012;7:1435-1445.
40. Tangri N, Inker LA, Tighiouart H, et al. Filtration markers may have prognostic value independent of glomerular filtration rate. J Am Soc Nephrol. 2012;23:351-359.
41. Cheung CL, Lam KS, Cheung BM. Serum beta-2 microglobulin concentration predicts cardiovascular and all-cause mortality. Int J Cardiol. 2013;168:4811-4813.
42. Christensson A, Ash JA, DeLisle RK, et al. The impact of the glomerular filtration rate on the human plasma proteome. Proteomics Clin Appl. 2018;12(3):e1700067.
43. Xhakollari L, Jujic A, Molvin J, et al. Proteins linked to atherosclerosis and cell proliferation are associated with the shrunken pore syndrome in heart failure patients. Proteomics Clin Appl. 2021;2000089.
44. Arkill KP, Qvortrup K, Starborg T, et al. Resolution of the three dimensional structure of components of the glomerular filtration barrier. BMC Nephrol. 2014;15(1):24. https://doi.org/10.1186/1471-2369-15-24
45. Öberg CM, Lindström M, Grubb A, Christensson A. Potential relationship between eGFRcystatin C/eGFRcreatinine-ratio and glomerular basement membrane thickness in diabetic kidney disease. www.medrxiv.org/content/10.1101/2020.12.16.20248179v1

How to cite this article: Grubb A. Glomerular filtration and shrunken pore syndrome in children and adults. Acta Paediatr. 2021;00:1–6. https://doi.org/10.1111/apa.15846