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COMMENTARY

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Should we need more sensitive early diagnostic markers in children with congenital solitary functioning kidneys?

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Life with a solitary functioning kidney (SFK) may not be similar to living with two kidneys. SFK carries out the function normally undertaken by two kidneys.

In their study, Kasap-Demir et al[1] included 36 children with SFK and 36 healthy controls. So far, no other study on vascular stiffness and central blood pressure (BP) parameters had been conducted in children and adolescents with congenital SFK. Herein, the authors describe that children with congenital SFK have additional risk for hypertension, arterial stiffness, and renal impairment. Early diagnostic markers such as ambulatory blood pressure measurements (ABPM), arterial stiffness indices pulse wave velocity (PWV), and central blood pressure (cBP) could be very useful tools during the follow-up.

Congenital SFK is more common than previously thought. This abnormality includes multicystic dysplastic kidney and/or unilateral renal aplasia/agenesis and may be associated with defects in the remaining kidney and urinary tract, which could further aggravate kidney function. Other rare associated abnormalities that fall within the context of a syndrome are nail patella syndrome or the branchio-oto-renal syndrome. Congenital SFK is expected in approximately one in every 1000-1400 births.[2] In spite of this, about 38% of cases of unilateral renal agenesis are missed. However, routine ultrasound assessment of the neonate could lead to the recognition of such congenital abnormalities.

SFK represents a unique model of a 50% renal mass reduction due to a theoretically 50% lower nephron number on average,[3] and patients are prone to develop problems later in life. SFK and congenital renal mass reduction in children result in a lower estimated glomerular filtration rate (eGFR).[4] Family history is considered a risk factor for more severe kidney failure.[5]

Being born with a SFK in childhood results in renal impairment before adulthood in over 50% of those affected.[6] The low number of nephrons increases the risk for cardiovascular (CV) and progressive renal disease.[7,8] Indeed, in the study of Kasap-Demir et al,[1] eGFR levels were significantly lower in the SFK group. The mechanisms that result in kidney injury in patients with a low number of nephrons are only partly understood. It is suggested that a low number of nephrons cause hemodynamic changes in the remaining glomeruli. In response to a reduction in kidney mass, the remaining kidney undergoes compensatory kidney growth with an unfavorable outcome in the long run. Compensatory hypertrophy results in an immediate increase in blood flow.[9] Higher amino acid content in the proximal tubules, direct activation of mTORC1, ribosome biogenesis, and protein synthesis are among the mechanisms that modulate cell growth and renal hypertrophy.[10] The increase in size of the glomeruli and kidney tubules leads to the maximal reabsorptive function and sodium handling in order to increase GFR[11] and preserve glomerulotubular balance.[12] This compensation increases GFR up to a value, which is approximately 75% of the normal value for two kidneys[13] and reaches its peak at a later time, at around the age of 8-10 years.[14] In humans, the long-term effects of hypertrophy and hyperfiltration are still insufficiently known. It is suggested that the increased glomerular pressure may be accounted similar to the mechanism of diabetic or obesity-induced hyperfiltration. Over time, compensatory mechanisms may contribute to hypertension and proteinuria, which gradually result in focal segmental glomerulosclerosis and a further nephron loss. This vicious circle within kidney injury ends in renal failure[15] (Figure 1).

For patients with congenital SFK, it was estimated that the median time to renal injury was 14.9 years.[16] A proportion of 38.1% of children with SFK developed renal injury at the median age of 11.0 years.[17] Additionally, the coexistence of congenital kidney in these patients increased the risk of stage 2 to 5 chronic kidney disease (CKD).[18] About 20%-40% of patients with a SFK require renal replacement therapy by the age of 30 years.[18,19] In another study, approximately 30% of enrolled children with SFK exhibited

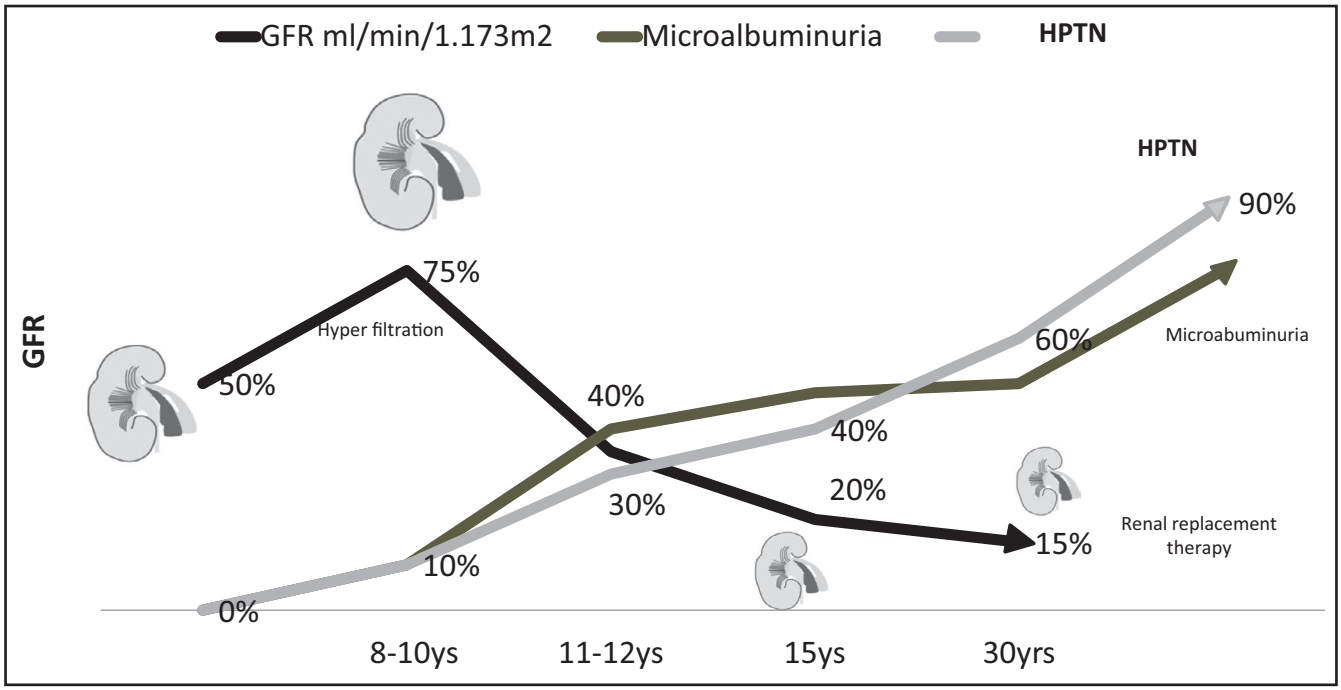

FIGURE 1 Congenital SFK solitary functioning kidney over time. GFR, glomerular filtration rate; HPTN, hypertension; SFK, solitary functioning kidney

indicators of renal injury by the age of 10 years and more than 50% of the children developed signs of renal injury by the age of 18 years.[16] Creatinine levels, recurrent urinary tract infection, and contralateral renal length are the predictors of an increased risk for renal injury.[20] There is a lack of sensitive early diagnostic markers that are necessary to differentiate patients with increased risk and to intervene at an earlier time point than after the onset of irreversible glomerular damage.

Children with abnormalities of a SFK often have hypertension.[21] Half of them will develop hypertension by the age of 18 years.[18] Approximately, a 20% reduction in nephron number is associated with increased BP levels followed by proteinuria and glomerulosclerosis.[18] In the study of Kasap-Demir et al,[1] ABPM was proven to be a useful tool for the screening of hypertension in children with SFK even if laboratory and imaging assessment is otherwise normal. The study showed that with the use of ABPM, the risk of hypertension increased by 6 times.[1] ABPM monitoring in patients with SFK reveals that one in five children has hypertension.[22] Additionally, a high rate of masked hypertension could also be diagnosed.[22] Using ABPM, Zahav et al[23] found that children with SFK had higher systolic BP than the controls. ABPM revealed the absence of dipping in diastolic and/or systolic BP in 82% of the patients with SFK.[24] In children with congenital solitary kidney, an inverse correlation between the renal size of the remnant kidney and mean ABPM has been found.[25] This finding reinforces the knowledge that reduced nephron mass is associated with elevated BP in adulthood, as suggested in research.[7] ABPM has been advised to be applied to all cases of SFK, being, also, a useful tool for the follow-up periods.

The rate of microalbuminuria, in the study of Kasap-Demir et al,[1] was similar among the investigated groups. In another study, microalbuminuria and hypertension were present in 50% of patients with SFK at 9 years of age.[4] It is fairly well established that microalbuminuria excretion is an early indicator of hyperfiltration injury. The presence of microalbuminuria suggests that a mild renal dysfunction may develop later in life and should always be measured.

Central BP measurement is superior to brachial BP measurement in determining CV risk in young adults.[26] The prognostic value of cBP has been recognized by expert consensus,[27] and cBP measures had at least the same power as ABPM in predicting end-organ damage.[28] In the study of Kasap-Demir et al,[1] cBP values were higher in patients with congenital SFK. Thus, the evidence that cBP levels are of higher prognostic significance compared with brachial BP levels in SFK patients increased.

Accelerated arterial stiffness represents an important mechanism that may damage major target organs including heart, brain, and kidneys. It is a functional marker of CKD arteriopathy; thus, a test, which could quantify the effects of risk factors on vasculature, should be carried out, to assess arterial health in children. Arterial stiffness measurement may distinguish those patients at an elevated risk of kidney injury and CV complications.[15]

PWV is currently the gold standard of arterial stiffness assessment, but its measurement in children is challenging, due to technical difficulties and physiologic aspects related to growth and to poor standardization between algorithms for calculating PWV.[29] Data about PWV in the pediatric CKD population remain relatively scarce and largely come from small case-control studies. Studies in children with CKD do not reveal

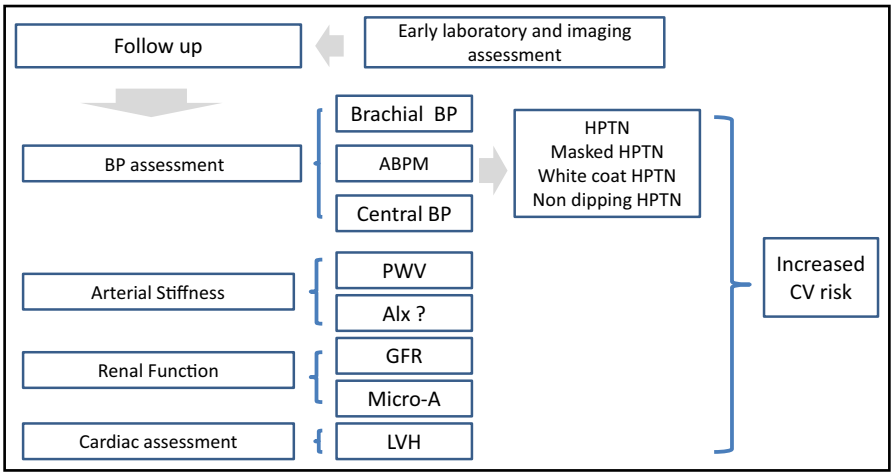

FIGURE 2 SFK monitoring for TOD. ABPM, ambulatory blood pressure measurement; AIx, augmentation index; BP, blood pressure; CV, cardiovascular; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; Micro-A, microalbuminuria; PWV, pulse wave velocity; SFK, solitary functioning kidney; TOD, target organ damage [Color figure can be viewed at wileyonlinelibrary.com]

direct associations between eGFR and PWV.[30] No studies have been conducted on vascular stiffness in patients with SFK. Kasap-Demir et al[1] suggest that determination of cBP and PWV would be useful indicators in children with SFK. The predictive value of the aforementioned measurements appears to outweigh that of conventional BP measurements.

In children, oscillometric pulse wave analysis (PWA) provides valid measures of cBP and arterial wave reflection and may be suitable for monitoring CV risk, as shown in children aged 8-10 years.[31] On the contrary, limited data exist exploring the use of augmentation index (AIx) in children. Accelerated arterial stiffness in childhood may also have a predictive value of CV outcomes in adult life.[29] Arterial stiffness indicates premature atherosclerosis.[31] The later begins early in the first decade of life, while its clinical manifestations are present in adulthood. The process accelerates arterial stiffening over time, and it is further deteriorated with the existence of comorbidities such as dyslipidemia, diabetes, or obesity.[31]

In CKD patients, hypertension increases pulsatile wall stress in arteries and contributes to progressive elastin fragmentation.[32] Structural changes in the arterial wall are characterized by abnormal vascular remodeling and progressive arterial calcifications. In children with kidney dysfunction, arterial stiffness is also associated with mineral-bone disease and related factors that may play a central role in arterial structural alterations.[29] Additionally, factors, such as oxidative stress and chronic inflammation, may also accelerate vascular damage.[29]

Prevalence of left ventricular hypertrophy (LVH) in adolescents increases with increasing BP level.[33] Optimal BP percentile associated with LVH in youth is still unknown. Kasap-Demir et al[1] did not observe any increase in left ventricular mass index (LVMI) between study groups. Arterial stiffness contributes to increased LV afterload, which can result in LV remodeling and LVH.[34] Higher PWV is associated with LV remodeling, and reduced LV systolic and diastolic function.[34] PWV was also correlated with LVMI in children with autosomal dominant polycystic kidney disease.[35]

A screening in every individual with a SFK appears to be imperative, starting from infancy (Figure 2). Lifelong monitoring of all children with an SFK is needed and should be easy to perform. The assessment of risk factors in congenital SFK patients is an interesting approach, mainly with accurate noninvasive tools. It is important to quantify the presence and severity of subclinical arterial disease and to evaluate the remote risk of overt CV disease development. Thus, BP monitoring with ABPM should be recommended. Additionally, measuring early changes in the arterial system, such as cBP and PWV, is considered a useful procedure, which may shed further light on the long-term prognosis. Microalbuminuria and GFR measurement should be proposed for better kidney function assessment. If physicians perform medical care properly, perhaps no other early diagnostic markers for the patients with SFK will be needed.

Intensification of lifestyle modification and weight loss efforts should be recommended. Children with a SFK may benefit from a reduced salt intake. Sport participation should be stimulated rather than limited. Comorbidities such as obesity, metabolic disturbances, hyperlipidemia, and anemia can impair the long-term renal function and should be treated and corrected. Such an assessment can be reasonably proposed.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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REFERENCES

1. Kasap-Demir B, Soyaltún E, Arslansoyu-Hamlar S, et al. Cardiovascular risk assessment in children and adolescents with congenital solitary kidneys. *J Clin Hypertens*. 2021;23(2):245–252.
2. Cochat P, Febvey O, Bacchetta J, Berard E, Cabrera N, Dubourg L. Towards adulthood with a solitary kidney. *Pediatr Nephrol*. 2019;34(11):2311-2323.

3. Argueso LR, Ritchey ML, Boyle ET Jr, Milliner DS, Bergstralh EJ, Kramer SA. Prognosis of patients with unilateral renal agenesis. *Pediatr Nephrol*. 1992;6(5):412-416.
4. Schreuder MF, Langemeijer ME, Bokenkamp A, Delemarre-Van de Waal HA, Van Wijk JA. Hypertension and microalbuminuria in children with congenital solitary kidneys. *J Paediatr Child Health*. 2008; 44(6):363-368.
5. Xu Q, Wu H, Zhou L, et al. The clinical characteristics of Chinese patients with unilateral renal agenesis. *Clin Exp Nephrol*. 2019;23(6):792-798.
6. Schreuder MF. Life with one kidney. *Pediatr Nephrol*. 2018;33(4):595-604.
7. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med*. 2003;348(2):101-108.
8. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis*. 1994;23(2):171-175.
9. Chen JK, Nagai K, Chen J, et al. Phosphatidylinositol 3-kinase signaling determines kidney size. *J Clin Invest*. 2015;125(6):2429-2444.
10. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell*. 2012;149(2):274-293.
11. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int*. 1996;49(6):1774-1777.
12. Wasilewska A, Zoch-Zwierz W, Jadeszko I, et al. Assessment of serum cystatin C in children with congenital solitary kidney. *Pediatr Nephrol*. 2006;21(5):688-693.
13. Baudoin P, Provoost AP, Molenaar JC. Renal function up to 50 years after unilateral nephrectomy in childhood. *Am J Kidney Dis*. 1993;21(6):603-611.
14. Westland R, Schreuder MF, Bokenkamp A, Spreeuwenberg MD, van Wijk JA. Renal injury in children with a solitary functioning kidney–the KIMONO study. *Nephrol Dial Transplant*. 2011;26(5):1533-1541.
15. McArdle Z, Schreuder MF, Moritz KM, Denton KM, Singh RR. Physiology and pathophysiology of compensatory adaptations of a solitary functioning kidney. *Front Physiol*. 2020;11:725.
16. Westland R, Kurvers RA, van Wijk JA, Schreuder MF. Risk factors for renal injury in children with a solitary functioning kidney. *Pediatrics*. 2013;131(2):e478-e485.
17. Kolvek G, Podracka L, Rosenberger J, Stewart RE, van Dijk JP, Reijneveld SA. Solitary functioning kidney in children–a follow-up study. *Kidney Blood Press Res*. 2014;39(4):272-278.
18. Schreuder MF, Nyengaard JR, Fodor M, van Wijk JA, Delemarre-van de Waal HA. Glomerular number and function are influenced by spontaneous and induced low birth weight in rats. *J Am Soc Nephrol*. 2005; 16(10):2913-2919.
19. Sanna-Cherchi S, Ravani P, Corbani V, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney Int*. 2009;76(5):528-533.
20. Poggiali IV, Simoes E Silva AC, Vasconcelos MA, et al. A clinical predictive model of renal injury in children with congenital solitary functioning kidney. *Pediatr Nephrol*. 2019;34(3):465-474.
21. Seeman T, Patzer L, John U, et al. Blood pressure, renal function, and proteinuria in children with unilateral renal agenesis. *Kidney Blood Press Res*. 2006;29(4):210-215.
22. Westland R, Schreuder MF, van der Lof DF, et al. Ambulatory blood pressure monitoring is recommended in the clinical management of children with a solitary functioning kidney. *Pediatr Nephrol*. 2014;29(11):2205-2211.
23. Mei-Zahav M, Korzets Z, Cohen I, et al. Ambulatory blood pressure monitoring in children with a solitary kidney - a comparison between unilateral renal agenesis and uninephrectomy. *Blood Press Monit*. 2001;6(5):263-267.
24. Zambaiti E, Sergio M, Baldanza F, Corrado C, Di Pace MR, Cimador M. Correlation between hypertrophy and risk of hypertension in congenital solitary functioning kidney. *Pediatr Surg Int*. 2019;35(1):167-174.
25. Dursun H, Bayazit AK, Cengiz N, et al. Ambulatory blood pressure monitoring and renal functions in children with a solitary kidney. *Pediatr Nephrol*. 2007;22(4):559-564.
26. Yano Y, Lloyd-Jones DM. Isolated systolic hypertension in young and middle-aged adults. *Curr Hypertens Rep*. 2016;18(11):78.
27. Avolio AP, Van Bortel LM, Boutouyrie P, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*. 2009;54(2):375-383.
28. Litwin M, Obrycki L, Niemirska A, Sarnecki J, Kulaga Z. Central systolic blood pressure and central pulse pressure predict left ventricular hypertrophy in hypertensive children. *Pediatr Nephrol*. 2019;34(4):703-712.
29. Azukaitis K, Jankauskiene A, Schaefer F, Shroff R. Pathophysiology and consequences of arterial stiffness in children with chronic kidney disease. *Pediatr Nephrol*. 2020. https://doi.org/10.1007/s00467-020-04732-y [Epub ahead of print]
30. Schaefer F, Doyon A, Azukaitis K, et al. Cardiovascular phenotypes in children with CKD: the 4C study. *Clin J Am Soc Nephrol*. 2017;12(1):19-28.
31. Zanoli L, Mikhailidis DP, Bruno RM, et al. Aortic stiffening is an extraintestinal manifestation of inflammatory bowel disease: review of the literature and expert panel statement. *Angiology*. 2020;71(8):689-697.
32. Mitchell GF. Arterial stiffness and hypertension: chicken or egg? *Hypertension*. 2014;64(2):210-214.
33. Urbina EM, Mendizabal B, Becker RC, et al. Association of blood pressure level with left ventricular mass in adolescents. *Hypertension*. 2019;74(3):590-596.
34. Ohyama Y, Ambale-Venkatesh B, Noda C, et al. Association of aortic stiffness with left ventricular remodeling and reduced left ventricular function measured by magnetic resonance imaging: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging*. 2016; 9(7). https://doi.org/10.1161/CIRCIMAGING.115.004426e004426 [Epub ahead of print]
35. Karava V, Benzouid C, Hogan J, Dossier C, Denjean AP, Deschenes G. Early cardiovascular manifestations in children and adolescents with autosomal dominant polycystic kidney disease: a single center study. *Pediatr Nephrol*. 2018;33(9):1513-1521.

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