



Ukrainian Journal of Nephrology and Dialysis

Scientific and Practical, Medical Journal

Founders:

- State Institution «Institute of Nephrology NAMS of Ukraine»
- National Kidney Foundation of Ukraine

ISSN 2304-0238;

eISSN 2616-7352

Journal homepage: <https://ukrjnd.com.ua>

Nephrology School

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doi: 10.31450/ukrjnd.3(71).2021.08

Advanced diagnostic techniques for paediatric chronic kidney disease in a developing country: A narrative review

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Citation:

Ndu IK, Ohayi SR, Edelu BO. Advanced diagnostic techniques for paediatric chronic kidney disease in a developing country: A narrative review. Ukr J Nephrol Dial. 2021;3(71):67-75. doi: 10.31450/ukrjnd.3(71).2021.08.

Abstract: *Chronic kidney disease (CKD) is described as a complex and progressive condition that arises from both non-communicable diseases (NCD) and communicable diseases (CD). Approximately a tenth of adults are affected worldwide, but the global prevalence of paediatric CKD remains unknown. Unfortunately, advanced diagnostic techniques and interventions are not readily available in most developing countries. This review seeks to create more awareness about paediatric CKD in a developing country like Nigeria and the need to intensify efforts to make new technologies for its diagnosis available and more affordable.*

Article history:

Received July 15, 2021

Received in revised form

July 28, 2021

Accepted August 05, 2021

Keywords: *diagnostic techniques, paediatric chronic kidney disease.*

Conflict of interest statement. The authors declare no competing interests.

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УДК 616.61-036.12-053.2-07

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Передові методи діагностики хронічної хвороби нирок у дітей в країнах, що розвиваються: огляд літератури

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Резюме: Хронічна хвороба нирок (ХХН) є тяжким прогресуючим захворюванням, яке може ускладнювати перебіг як неінфекційних захворювань, так і інфекційних захворювань. Приблизно десята частина дорослого населення світу страждає на ХХН, але поширеність ХХН у дітей залишається невідомою. На жаль, передові методи діагностики та лікування недоступні у більшості країн, що розвиваються. Цей огляд має на меті підвищити обізнаність щодо ХХН у Нігерії та активізувати зусилля, спрямовані на покращення доступності нових діагностичних та лікувальних підходів.

Ключові слова: діагностичні методи, педіатрична хронічна хвороба нирок.

Introduction. Chronic kidney disease (CKD) is described as a complex and progressive condition that arises from both non-communicable diseases (NCD) and communicable diseases (CD) [1, 2]. Ultimately, it culminates in end-stage renal disease (ESRD) after passing through five distinct phases at a pace determined by the presence of comorbidities [2-4]. Approximately a tenth of adults are affected worldwide, but the global prevalence of paediatric CKD remains unknown [5, 6]. However, it is relatively low among the paediatric age group compared to adults as suggested by available population-based data [5, 7-10]. It is particularly challenging to assess the impact of pediatric kidney disease in Nigeria because of the time gaps between the few available studies, which are primarily hospital-based [11].

The rising number of non-communicable diseases worldwide has been linked to the global surge in CKD prevalence [2, 5, 12, 13]. Most children with CKD have congenital or inherited kidney disorders, with obstructive uropathy reported as the commonest in US children [7, 12, 14]. Similarly, Ladapo et al. in Nigeria reported congenital anomalies of the kidney and urinary tract (CAKUT) as the leading cause of CKD [11]. More often than not, as countries become more advanced, diseases tend to move from infectious to chronic conditions [15]. A similar pattern has become more noticeable among a lot of impoverished countries [2]. Although infectious causes of CKD in

low to medium-income countries (LMICs) are still less common than the non-communicable causes, they remain a major cause of public health concern and contribute significantly to CKD [5, 13, 16, 17].

Although CKD occurs more commonly in adults and aged individuals [5, 6, 18], it is now evident that its aetiology can be traced back to prenatal events [12, 19, 20]. For instance, uteroplacental insufficiency or maternal malnutrition may result in small for gestational age infants who may have a paucity of nephrons and develop increased blood pressure with the potential risk of progressive renal injury [21]. Knowledge of these possible risk factors may facilitate measures that can reduce the rate of development of chronic kidney disease [12].

As research to understand the role of these risk factors continues, genetics is being explored for associations with CKD, which may provide possible interventional and prognostic tools for determining genetic risk factors for CKD progression in children [7].

Accurately calculating the glomerular filtration rate (GFR) is key to staging CKD [7, 22]. There is agreement about the inaccuracy of measurement of GFR by a timed urine collection because of variable creatinine clearance [7, 22]. While GFR measurement by inulin clearance is accepted as the gold standard, and it is an arduous assay to perform, particularly in children [7, 23]. Thus, innovative methods of GFR estimation, such as the iohexol plasma disappearance method, validated by the Chronic Kidney Disease in Children (CKiD) study in North American pediatric nephrology centers, are now used to help clinicians assess those at risk for progressive kidney injury [12, 23-26].

Due to the correlative nature of renal pathology diagnosis, other investigation modalities such as electron microscopy (EM) and antibodies to localize antigens in tissue sections from percutaneous needle

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biopsies are essential [3, 27, 28]. Unfortunately, because of multiple challenges in developing nations, most renal biopsies are reported with light microscopic examination alone [27-29].

Paediatric cases of chronic kidney disease (CKD), especially those from LMICs who often have unrecognized and untreated CKD, progress to ESRD [27, 29]. This requires life-saving renal replacement therapy (RRT), which unfortunately is very expensive and therefore unaffordable in most of these developing countries [3, 5, 30-32].

Unfortunately, these advanced diagnostic techniques and interventions are not readily available in most developing countries. Therefore, this review was done by the authors to create more awareness about the need for early identification and prevention of known risk factors of CKD while intensifying efforts to make new technologies for its diagnosis available and more affordable.

Description of the literature search. The literature search was conducted through PubMed and Google web search for articles on pediatric chronic kidney disease. The following search terms were employed: "chronic renal disease definition," "chronic renal disease diagnosis," "chronic renal disease in Nigeria," "chronic renal disease challenges." Studies relevant to the objectives of this narrative review were subsequently selected and reviewed.

Pathophysiology of paediatric chronic kidney disease. The pathological features accompanying paediatric chronic kidney diseases are complex and interrelated by their pathophysiologic mechanisms. As such, this clinical syndrome of paediatric CKD is seen as a definite class of illness [33]. By nature, PCKD is associated with long-term complications with resulting in higher mortality and lower life expectancy than in the general population [34]. Certain general physiologic principles of renal function underlie the various injuries associated with CKD, namely: i) high perfusion rate of the kidney, which exposes the kidney to a higher amount of circulating harmful substances ii) high intra- and transglomerular pressure necessary for effective glomerular filtration expose glomerular capillaries to haemodynamic injuries. iii) interconnection between the glomerular and peritubular capillaries facilitates the transfer of glomerular injuries to the tubulointerstitial space. iv) nephron as an integrated complex that damages one part likely to affect other components [34]. Ultimately, the derangement in renal function progress to ESRD whilst also leading to various pathophysiologic problems in different organ systems of the body, which includes the following.

Poor growth/Growth failure. Typically, children with CKD have growth derangement [35, 36]. A 2006 North American Paediatric Transplant Cooperative Study (NAPTCS) showed that over 35% of children with PCKD attained only a final height below the third percentile or exhibited -1.88 median standard deviation score (HtSDS) and that glomerular filtration

rate correlated positively with HtSDS [37, 38]. Growth retardation is also positively correlated with the age of onset of Paediatric CKD/age of enrolment with average HtSDS for respective age groups with scores in infancy, young childhood and adolescence as -2.33, -1.65 and -0.93, respectively [38].

In general, growth retardation in CKD is due to the following conditions: CKD mineral and bone diseases (CKD-MBD) through poor bone growth etc., metabolic acidosis by degradation of proteins, endogenous production or corticosteroids, and suppression of appetite leading to malnutrition; chronic anaemia which causes poor appetite and cardiac dysfunction and fluid and electrolyte disturbances [35, 39-41]. Other associated factors include cardiac complications, end-organ resistance to GH and abnormalities of the GH-IGF-1 pathway, and the malnutrition-inflammation complex [41, 42]. According to Rees [35], in infancy and early childhood, nutrition affects growth much more than the GH-IGF-I axis, suggesting that malnutrition may be the most critical factor contributing to growth impairment at that age. In children who develop CKD at infancy, boosting calorie intake during early childhood leads to improved growth [35]. As summarized by Silverstein [43], in addition to impairment of general development in PCKD, dysregulation of the hypothalamic-pituitary axis with resultant hypergonadotrophic hypogonadism leads to delayed puberty for up to 2 years [36]. This affects children requiring renal transplants before age 13 the most [44, 45].

Bone disease [chronic kidney disease-mineral and bone disease (CKD-MBD)]. Bone disease is one of the earliest pathophysiologic problems to occur in paediatric CKD [42]. It occurs as part of a complex called chronic kidney disease-mineral and bone disease (CKD-MBD) characterized by one or more abnormalities of calcium, phosphate, parathyroid hormone and vitamin D metabolism, renal osteodystrophy (ROD), plus calcification of vascular or other soft tissue. ROD consists of abnormalities in bone histology, linear growth, strength, and pathological fractures [36, 42, 45].

Renal osteodystrophy of paediatric CKD follows a complex interaction between several factors, including derangement in the production of active vitamin D with resultant poor intestinal absorption of calcium and then secondary hyperparathyroidism with consequent mobilization of calcium from bones [36, 42, 43]. Also, renal function derangement leads to metabolic acidosis, which in turn blunts trophic effects of growth hormone on bones [36, 43]. Also, it reduces the renal generation of active vitamin D with resultant mobilization of Calcium from bones, thereby worsening bone disease [36, 43].

Other mechanisms of bone disease include the increase in circulating FGF23 following hyperphosphataemia from decreasing excretion of phosphate as a result of falling GFR. FGF23 causes bone

cysts, marrow fibrosis, and reduced or no production of bone marrow, known as osteitis fibrosa cystica [36, 42]. Prolonged stimulation of the parathyroid gland by prolonged hyperphosphataemia and hypocalcaemia will make the gland autonomous. This tertiary hyperthyroidism further worsens the mobilization of calcium from bones [36, 42].

Reduced Haemoglobin concentration/anaemia.

Anaemia is quite common in paediatric CKD patients, with prevalence increasing with the advancement of the disease [33, 42]. As summarized by Kaspar [36] and Becherucci [33], it occurs in 45% of cases and negatively affects outcomes, quality of life, and neurocognitive development and functions [46]. Unlike in adults, diagnosis of anaemia in paediatric CKD is not straightforward since diagnostic parameters depend on age range and sex [47].

The pathophysiologic mechanisms that lead to anaemia in paediatric CKD include decreased production and secretion of erythropoietin [36, 42, 48], reduced or no RBC production in osteitis fibrosa cystica [42] and red blood cell (RBC) fragility and high turnover of immature RBC associated with uremia [42, 49]. Other causes of anaemia include intestinal loss of RBC, which is highest in patients undergoing hemodialysis, blood loss to hemodialysis equipment and tubing, and loss of RBC-iron homeostasis [36].

Hypertension. Hypertension has been reported to occur very early in paediatric CKD, with an increasing prevalence as GFR worsens [50]. It is caused by salt retention that results from derangement of GFR and also by continuing renin secretion by the kidney in some diseases [42]. According to Becherucci's review [33], 54% of children with CKD had high blood pressure (HBP) when they enrolled in a CKiD study group study. In comparison, BP in 48% remained elevated despite antihypertensive treatment. In addition, the BP in these patients has characteristics associated with the increased cardiac morbidity in adulthood. HBP further damages the kidney, thus expediting a decline in renal function.

Cardiovascular disease is an important cause of mortality in paediatric CKD, conferring a 1000 times higher risk of death in ESRD than in age-matched non-ESRD children [36, 50, 51]. Cardiovascular complications begin early in PCKD and progress rapidly following the onset of dialysis [51]. A combination of hypertension causes PCKD-related cardiovascular disease, elevated circulating PTH, FGF 23, 25-OHvitD, and deposition of calcium phosphate in the heart and coronary artery [42, 50, 52]. The pathophysiologic mechanisms underlying PCKD CVD include left ventricular hypertrophy, endothelial dysfunction, and arterial thickening from uremia-induced medial calcification [42, 50, 53]. The leading cause of cardiovascular disease-related death in PCKD includes arrhythmias, valvular diseases, cardiomyopathy, and cardiac arrest [54].

Poor neurocognitive development and quality of life. As summarized by Becherucci et al. [33],

and Kaspar et al. [36], childhood-onset CKD leads to poor neurocognitive development and quality of life in adulthood. These patients have low physical, social, and health-related quality of life (HRQOL) parameters and exhibit low energy, weakness, daytime sleepiness, anxiety, and depression. GFR varies in direct proportion to HRQOL, while treatment with GH improves associated parameters also [55]. According to the CKiD study, a significant proportion of children with CKD has a risk for dysfunction in IQ, educational performance, and executive functioning of up to 1 standard deviation below the mean [46].

Comorbidities & other factors that affect CKD progression in children. Researchers have identified that certain factors are associated with the rapid progression of CKD to ESRD. As summarized by Kaspar et al. [36], these include severe proteinuria, glomerular aetiology, older age, non-Caucasian race, and presentation with stage 4 CKD, while for non-glomerular PCKD, the factors include dyslipidaemia, male gender, hypoalbuminaemia, urinary protein – creatinine ratio of >2mg/mg, and anaemia. Based on these identified factors, the risk for progression has been classified into low, medium, and high-risk groups with renal survival times of 135, 80, and 16.3 months. Other conditions which hasten the progression of CKD include hypertension [36, 56], concomitant cardiovascular disease, and puberty [57, 58].

Diagnosis of chronic kidney disease. Traditionally, blood and serum-based biochemical measurements of substances secreted through the kidney are used to diagnose renal diseases, including paediatric CKD. These tests have, over time, proven not to be sufficiently sensitive and specific for this purpose.

Nigeria, being a developing country, has several challenges, of which the availability of modern diagnostic equipment in our hospitals is not excluded. Most diagnoses of renal diseases in the healthcare facilities are clinical, with the support of the baseline investigations such as urinalysis, full blood count, serum and urinary electrolytes, urea and creatinine estimations, and the few available radiological imaging diagnostic equipment. Routine radiological imaging is only helpful for diagnosing gross anatomical abnormalities e.g., renal stones and other causes of obstruction, tumours, etc [59]. These limitations arise because of the nature of renal diseases. A variety of renal morphologic patterns can result in the same clinical syndrome e.g., nephritic syndrome from hereditary nephropathy, MPGN, IgA nephropathy etc.; nephrotic syndrome from minimal change disease, FSGS, membranous glomerulonephropathy while one disease may cause more than one distinct pattern of renal injury e.g., SLE can cause glomerular &/or parenchymal injuries. Also, different conditions can cause or be associated with one specific pathologic process e.g., SLE, HCV infection & proliferative GN [59, 60].

The implication of using such limited methods in the diagnosis of chronic kidney disease is the inability

to correctly identify the cause of the problem or the true nature and extent of the pathology. As such novel methods of diagnosis that can detect anatomical, molecular, and functional changes in the kidney are being developed and deployed in developed countries. Improved investigative techniques will afford the opportunity of early diagnosis, in which case reversible diseases can be treated; progression of CKD may be halted or slowed; comorbid conditions can be treated; renal replacement therapy can be arranged ahead of deterioration to end-stage kidney disease [61].

Novel diagnostic methods for chronic kidney disease:

Laboratory investigation/Biochemical testing.

Cystatin-C is progressively replacing creatinine as an endogenous marker for glomerular filtration function, having been found to have more reliability than creatinine [62].

Imaging. Imaging studies of the kidneys are used to study both anatomical, renal perfusion, and glomerular filtration abnormalities. As summarized by Thuman and Gueler [59], like USS used to study structural abnormalities, the more sophisticated imaging methods, namely Doppler imaging, CT scan, and MRI used to assess renal blood flow, also have their limitations. The contrast media for the first two are known to be nephrotoxic, while that for MRI causes nephrogenic systemic fibrosis in patients with CKD [59]. However, newer contrasts for MRI, namely gadobenate dimeglumine or gadobutrol, proven to be safe in CKD, have been developed [63, 64]. Additionally, arterial spin labeling (ASL), which uses magnetically tagged intrinsic water as a contrast for MRI, has also been designed for the evaluation of renal perfusion [65]. Also, Thuman and Gueler [59] summarized new modalities being used as follows:

1. Use of imaging probes: agents that can detect specific molecules or biologic processes as indicators of distinct kidney structural and functional abnormalities
2. Blood oxygen level-dependent (BOLD) MRI: determines tissue oxygenation and, therefore disease. Tissue relaxation rate, $R2^*$ is inversely proportional to tissue oxygen concentration. BOLD MRI has shown that $R2^*$ is higher in paediatric CKD patients than in the healthy population.
3. Dynamic contrast-enhanced (DCE) MRI: uses renal perfusion and glomerular filtration of gadolinium-based contrast agents (GBCAs) to assess CKD.
4. Sodium (^{23}Na) MRI: quantifies and localizes sodium in the kidney and other tissues. This technique has shown that there is high sodium concentration in tissues in people with end-stage renal diseases than in others.
5. Hyperpolarized MRI: uses specific hyperpolarized molecules to assess the transport and metabolic functions of the kidney. By using hyperpolarized ^{13}C pyruvate, the metabolism of pyruvate to lactate is altered in models of diabetic nephropathy.

6. Elastography (Acoustic radiation force impulse imaging): studies the stiffness of the kidney and, therefore degree of fibrosis by measuring the shear wave velocity (SWV) when an impulse is applied to a tissue. Elastography performed in CKD patients has shown that SWV correlated with the degree of kidney disease. MR elastography has been developed and is being standardized.
7. Diffusion-weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI): both MRI-based imaging methods use the direction of movement of water molecules in tissues to determine the degree of renal fibrosis.

Imaging facilities such as CT scans and MRI for diagnosis of renal and other diseases are available in the country but sparsely distributed and unaffordable to the average Nigerian. This has led to the limited use of these diagnostic facilities to diagnose chronic renal diseases in children.

Renal biopsy. Renal biopsy for CKD is usually a percutaneous procedure consisting of using specialized needles to obtain biopsies from the kidney. It is generally performed under ultrasound guidance where facilities are available. Indications for renal biopsy include nephrotic range renal impairment without a precise diagnosis by other methods, as a guide for management and prognostication of certain diagnosed conditions e.g., lupus nephritis, vasculitis etc. and in established diagnosis e.g., diabetic nephropathy but with unexplained deterioration in renal function [59, 61]. Examination of renal biopsy specimens by routine haematoxylin and eosin method has a minimal diagnostic value. Specialized techniques have therefore been developed, namely immunofluorescence staining and electron microscopy.

The situation in Nigeria. Despite the availability of these newer methods of diagnosis, most Nigerian researchers still diagnose chronic kidney disease based on the glomerular filtration rate of $<60 \text{ ml/min/1.73 m}^2$ for ≥ 3 months, Kidney Disease Outcomes Qualitative Initiative (KDOQI) diagnostic and staging criteria, and the International Study of Kidney Disease in Children guidelines. Imaging techniques such as computerized tomography scan (CT scan), ultrasonography, micturating cystourethrogram, intravenous urogram, and magnetic resonance imaging (MRI) are also employed in some cases. Pathologic abnormalities on percutaneous biopsy, presence of markers of damage in urine, blood, or congenital anomalies of the kidneys and urinary tract (CAKUT) are sometimes employed in diagnoses [11, 31, 66, 67]. The implication of the use of such limited methods in the diagnosis of chronic kidney disease is the inability to correctly identify the cause of the problem or the true nature and extent of the pathology.

It's also important to note that most Nigerians fund healthcare from out-of-pocket expenses despite the minimal income and over 70% living below the poverty line. This becomes a limiting factor to the use of

modern diagnostic facilities even in centres where they are available.

Despite these drawbacks, physicians managing children suspected to have chronic renal diseases should try and maximize the available basic investigative techniques in the country. Percutaneous biopsies should be done whenever indicated. This will enable researchers and paediatricians to know the prevalent causes of chronic renal diseases among children in our environment and thus help in finding preventive measures. The few available radiological imaging studies should be utilized whenever possible. This will help to properly define the scope and the cause of the CKD in some cases. The use of c-cystine should be encouraged in all facilities where children with CKD are managed to replace creatinine estimation. Finally, efforts to make these newer diagnostic facilities and methods available in all our tertiary healthcare centres should be vigorously pursued by all policymakers and authorities.

This will enable the country to catch up with the rest of the world in PCKD diagnosis and management.

Conclusion. In conclusion, advanced diagnostic techniques and interventions are not readily available for paediatric CKD in Nigeria. There is an urgent need for advocacy by health care providers to create more awareness about this condition. Public-private partnership arrangements are key to making new technologies for its diagnosis available and more affordable.

Conflicts of Interest. The authors report no conflicts of interest in this work

Contributions. This study was conceived by NIK, OSR and EBO. Abstract and Introduction were written by NIK. Pathophysiology and diagnosis of paediatric chronic kidney disease was written by OSR. The situation in Nigeria and conclusion were written by EBO. All authors reviewed the final draft of the paper. NIK, OSR, EBO are equal contributors.

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