METABOLIC AND ENDOCRINE COMPLICATIONS OF CHRONIC KIDNEY DISEASE IN CHILDREN

TO Bizerea-Moga[1,2], A Crăciun[1,2], P Tegian[2], A Velcelean[2], O Mărginean[1,2]

Abstract

Introduction: Pediatric CKD and the long-term complications not only have an impact on the child's health, but are also transforming this pathology into a worldwide health problem. Aim: To evaluate the metabolic and endocrine complications described in patients with CKD. Material and method: A four-year retrospective observational study was conducted between January 2015 and the December 2018, at "Louis Turcanu" Children's Clinical and Emergency Hospital. 41 pediatric patients, diagnosed with chronic kidney disease (CKD) were included. According to the etiology of CKD, patients were divided in two study groups: 22 patients (53.7%) with congenital anomalies of the kidney and urinary tract (CAKUT) and 19 patients (46.3%) with glomerular disease. Metabolic and endocrine complications if documented were recorded in all patients. Results: Dyslipidemia (47.7%) and hypertension (36.8%) were more prevalent in patients with glomerular disease whereas CAKUT more often associated mineral-bone disease (31.8%) and anemia (27.3%). Patients from the CAKUT group showed higher complication rates in end-stage CKD, 18.8% for both bone mineral disorder and anemia. Patients with glomerular disease had complications in early stages of CKD, predominantly represented by dyslipidemia (73.7%) and hypertension (52.6%). The highest prevalence of short stature was noted among end-stage CAKUT-CKD patients (22.7%), followed by stage 3 CAKUT-CKD (13.6%) patients. Conclusions: The main cause of CKD in children is represented by CAKUT. Anemia and mineral and bone disorder are the main complications in CAKUT-CKD, whereas glomerular disease primarily associates hypertension and dyslipidemia. Complications appear in early stages of glomerular disease - CKD and advanced stages of CAKUT-CKD. Short stature is more prevalent in advanced CKD stages.

Keywords: chronic kidney disease, congenital anomalies of the kidney and urinary tract, children, metabolic and endocrine complications

Introduction

Kidney Disease Improving Global Outcomes (KDIGO) defines chronic kidney disease (CKD) as a chronic pathology, result of a gradual loss of kidney function developing for more than 3 months, manifested by the following features: GFR <60 mL/min/1.73 m2 or structural damage of the kidney and urinary tract, identified by blood or urine studies, imaging tests or kidney biopsy [1].

CKD has become a major health problem over the last decade, due to its increasing incidence and prevalence. Primary causes of CKD in young children are represented by congenital anomalies of kidney and urinary tract (CAKUT), while tubular and interstitial glomerulopathies are predominant in children over the age of 10 years [2-5].

CKD is often clinically asymptomatic, especially in earlier stages. The symptoms can be subtle and frequently unspecific, making the diagnosis a real challenge for the clinician.

Growth impairment is one of the most common and perhaps the most noticeable CKD complication. The degree of the growth impairment correlates with GFR, and its severity increases as the age of onset is decreased. The risk factors that contribute to growth impairment are: metabolic acidosis, anemia, mineral and bone disorders and electrolyte imbalances. However, especially after early childhood, growth failure is mainly due to decreased bioavailability of somatotropin in uremia [7-9].

The mineral and bone disorder of CKD is a systemic disorder defined by the presence of disturbances of biohumoral markers or pathological findings on imaging tests or bone histology. The term renal osteodystrophy is exclusively used to define alterations of bone morphology. This complication is present in about 60-80% of children with CKD and is manifest after the loss of approximately 50% of the nephron population. CKD leads to alterations of mineral homeostasis characterized by imbalances of serum calcium (Ca), phosphorus (P), parathormone (PTH) and 1,25- Dihydroxyvitamin D3 levels. GFR decrease under 60 ml/min/1, 73 m2 determines phosphate retention, an increase in PTH secretion and suppression of calcitriol synthesis in the kidney [4, 10].

[1] "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2]1st Pediatric Clinic"Louis Turcanu" Children's Clinical and Emergency Hospital, Timisoara, Romania

E-mail: bizerea.teofana@umft.ro, craciun.adrian@umft.ro, paula.tegian@gmail.com, alexandra_velcelean@yahoo.com, omarginean@ymail.com

Common causes in children < 5 years old :	Common causes in children > 10 years old :
Malformative uropathies 25%	Glomerular nephropaties 33%
Hereditary nephrophaties 16%	• Focal segmental glomerulosclerosis • Proliferative endo- and exocapillary glomerulonephritis
• Cystinosis • Oxalosis • Alport Syndrome	Vascular nephrophaties 5%
Hypo-/ Dysplasia 17.6 %	• Hemolytic-uremic syndrome • Diabetes mellitus
• Cystic/ Noncystic • Segmental hypoplasia • Cystic kidney disease	• Hypertension • Renal vein thrombosis

Table 1. Etiolgy of CKD in children [6]

Study group	*Patient number*	*Endocrine and metabolic complications*	*Paraclinical investigations*
Congenital structural abnormalities of the kidney and urinary tract	22	➢ Growth impairment ➢ Systemic hypertension ➢ Anemia	➢ Anthropometric measurements, bone age ➢ Blood pressure ➢ Complete blood count, reticulocyte count, serum iron, ferritin, transferrin, serum erythropoietin
Glomerular disease	19	➢ Dyslipidemia ➢ Mineral and bone disorder	➢ Lipid panel ➢ Total calcium, ionized calcium, phosphate, intact parathyroid hormone from plasma

Table 2. Patient distribution in study groups according to the etiology of CKD

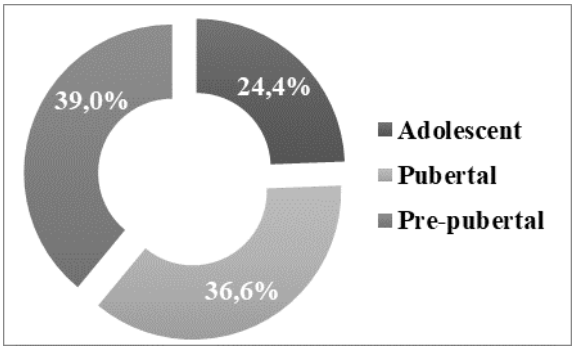

Fig. 1. Patient distribution according to age at time of study

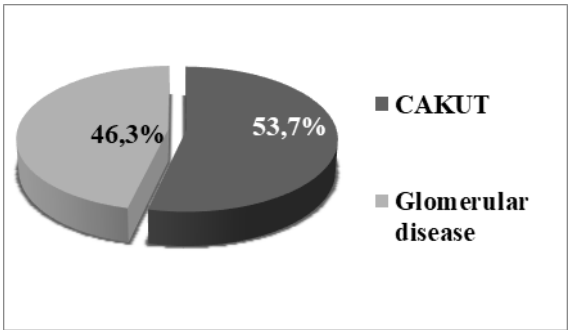

Fig. 2. Percentage distribution of patients according to etiology of CKD

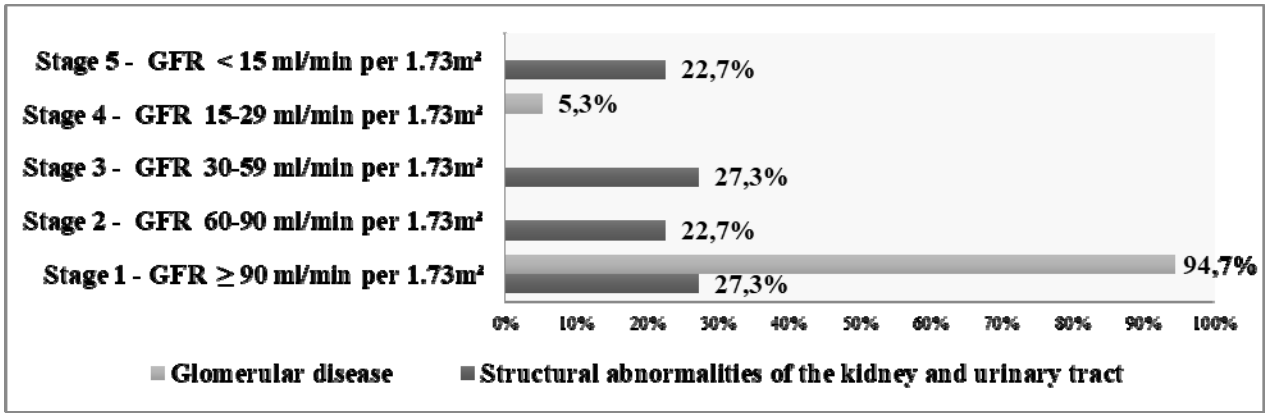

Fig. 3. Stages of CKD among studied patients according to GFR

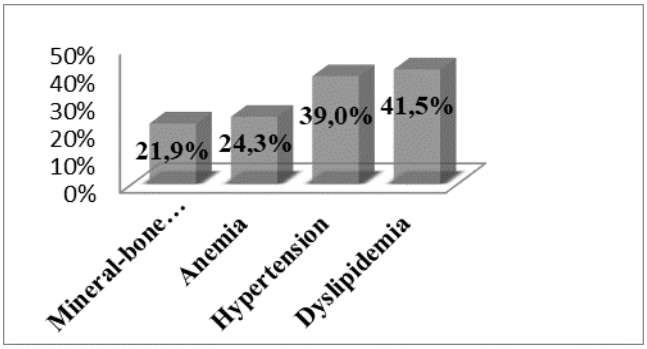

Fig. 4a. Endocrine and metabolic complications of CKD in the studied patients

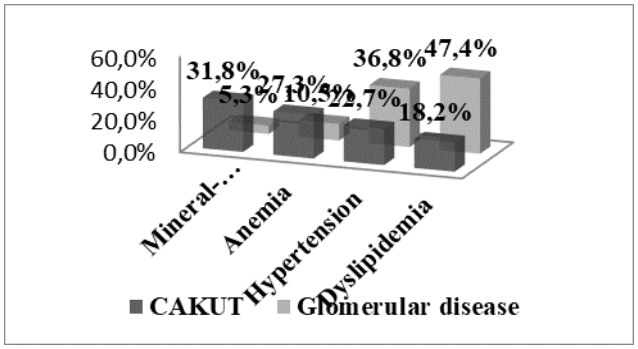

Fig. 4b. Percentage distribution of endocrine and metabolic complications in studied groups divided according to CKD etiology

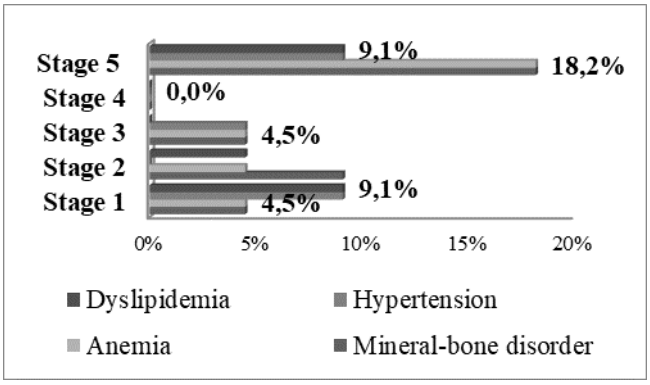

Fig.5a. Percentage distribution of complications according to CKD stages in patients with CAKUT

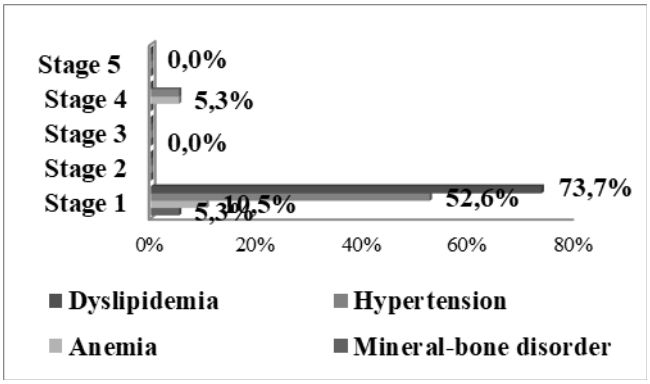

Fig.5b. Percentage distribution of complications according to CKD stages in patients with glomerular disease

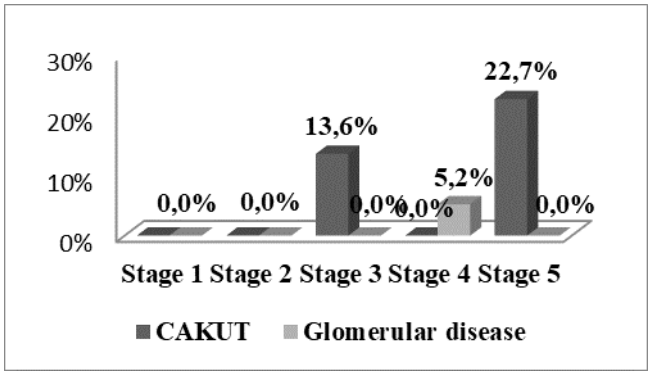

Fig. 6. Prevalence of short stature among studied patients

Anemia is a common complication in children with CKD and is defined as hemoglobin (Hb) levels under the 5th percentile relative to age and sex. The prevalence of anemia increases with CKD progression. Renal anemia is present in 73% of stage 3, and in over 93% stage 5 CKD cases [11]. Although anemia has a complex etiopathogenesis resulting from the interaction of multiple factors, the principal role is played by erythropoietin (EPO) deficiency, especially in advanced stages of CKD [12]. The decreased EPO synthesis at cellular level is caused by interstitial fibrosis that leads to irreversible loss of kidney function. Renal fibroblasts or EPO producing pericytes are transformed into myofibroblasts and lose synthesis function. The anemia of CKD is typically normocytic, normochromic, and hypoproliferative. Other causes include iron deficiency, chronic inflammation, malnutrition, secondary hyperparathyroidism and uremia [13].

The typical CKD dyslipidemia is hypertriglyceridemia. There is an inversely proportional relationship between GFR and triglyceride (TG) and total cholesterol levels, but a direct proportional one with high density lipoprotein (HDL) levels. The abnormally high TG levels are attributed to overproduction, due to increased hepatic VLDL synthesis associated with a decreased catabolism. Furthermore, the levels of apolipoprotein C-III, a direct inhibitor of lipase, are increased in uremia, causing a rise in TG values. Secondary hyperparathyroidism plays an additional role in the reduction of VLDL catabolism. Although, LDL levels are within normal range in CKD, the particles tend to be smaller, denser and more atherogenic [14, 15].

In children, 70% of hypertension cases are secondary and 50-80% of these are caused by renal parenchymal disease. Thus, arterial hypertension can be the first sign of CKD in children. Hypertension, defined as arterial blood pressure values over the 90th percentile relative to age, sex and height, can manifest even in early stages of CKD and is negatively correlated to GFR [16]. Recent randomized studies have shown that maintaining the tensional values below the 50th percentile, delays the progression of CKD [3, 17].

Aim of the study

The purpose of the study was to evaluate the metabolic and endocrine complications described in patients with CKD.

Materials and Methods

A retrospective observational study was conducted over a four-year period (1st of January 2015 and the 31th of December 2018), at the 1st Pediatric Clinic of "Louis Turcanu" Children's Clinical and Emergency Hospital. Medical records of pediatric patients aged 0-18 years diagnosed with CKD were analyzed. An electronic registry composed of anonymized patient data was created by searching individual patient files. 41 patients were divided into two study groups according to the cause of CKD, respectively 22 patients with CAKUT and 19 patients with glomerular disease. Anthropometric measurements, blood pressure and bone age were recorded. Blood studies including anemia, lipid and bone metabolism panel were documented in all subjects, as shown in Table 2.

Results

The distribution of patients from the study group according to age is shown in Figure 1. The highest

percentage was represented by pre-pubertal children (39 %) followed closely by pubertal patients (36.6%).

As shown in Figure 2, there are no significant differences between the study groups resulting from the distribution of patients according to the etiology of CKD. CAKUT was the underlying cause in 54% and glomerular disease in 46% of cases.

Figure 3 highlights the distribution of patients according to CKD stages based on GFR values. The study group consisting of patients with CAKUT had a more severe impairment of renal function translated by a higher percentage of patients with end-stage CKD (22%). In comparison, only 5% of the patients with glomerular disease have reached fourth stage and none end-stage CKD.

Figures 4a and 4b show the incidence of CKD complications among the patients included in the study. A specificity of the complications that have arisen depending on the etiology of CKD is noted.

In Figures 5a and 5b, the distribution of complications according to CKD stages is shown. According to the underlying cause for CKD, specific patterns can be noticed. Bone mineral disorder and anemia, both with the highest prevalence of 18.2% in end-stage CKD in patients with CAKUT. Dyslipidemia (73.7%) and hypertension (52.6%) are noted in stage 1 CKD in patients with glomerular disease.

Discussion

Although progress has been made in recent years in the diagnosis, monitoring, and treatment in children, CKD still represents a „silent epidemic" in this age-group. The initial stages of CKD are usually asymptomatic leading to late discovery and guarded prognosis of the disease.

This study shows a relatively balanced age-related distribution of subjects in three distinctive groups: 39% pre-pubertal, 36.6% pubertal and 24.4% adolescent patients.

Data form literature records a correlation between socio-economic status and the etiology of CKD. In a study carried out in France on a group of 127 children with CKD, 68.5% were shown to have underlying CAKUT, and 30.7% acquired nephropaties [18]. In a retrospective study conducted in Iran, the main cause of CKD in children was glomerular disease (34%), followed by reflux nephropathy (16.7%) [6]. Similar data was published in a review from Nigeria, which confirms glomerulopathies as the leading cause of CKD, in 53.3% of 45 end-stage cases evaluated along 15 years [19]. No significant difference between the two main causes of CKD were noted in this study. CAKUT was diagnosed in 53.7% and glomerular disease in 46.3% of children admitted for CKD, at the Emergency Hospital for Children "Louis Turcanu" Timisoara.

Most of the epidemiological information on CKD and associated metabolic and endocrine complications, comes from registries of end-stage patients requiring renal replacement therapy (RRT). Data on early stages of CKD are still limited. Complications of CKD in both early and end stages were observed in the conducted study. Comparative analysis of GFR in the two study groups revealed more severe kidney damage, in patients with CAKUT. Thus, 22.7% of these patients had been diagnosed with end-stage CKD, and a cumulative percentage of over 70% of patients demonstrated impaired renal function, translated by decreased GFR. By comparison, 94.7% of patients with glomerular disease showed GFR within normal ranges at the time of study. A study conducted by Deleau and colleagues demonstrated that although initial GFR is better at onset in glomerular disease, the decrease of kidney function occurs more rapidly in these cases [18].

As can be seen in Figure 4a, the main complication of CKD was dyslipidemia (41.5%), followed by hypertension (39.0%), anemia (24.3%) and bone mineral disease (21.9%). Figure 4b highlights the distribution of complications according to the etiology of CKD. Thus, it can be noticed that dyslipidemia (47.7%) and hypertension (36.8%) are complications with the highest prevalence in the glomerulopathy group, totaling more than 80 % of cases, compared to anemia and mineral-bone disease, which add up to only 15.8 %. These data are consistent with recent clinical trials, such as the Taiwan Pediatric Renal Collaborative Study conducted in 2016 by the working group of Chou and collaborators [20]. In contrast, CAKUT more often associated mineral-bone disease (31.8%) and anemia (27.3%). In this study group, the complications were more evenly distributed. Hypertension and dyslipidemia had a lower prevalence of 21% and 17%, respectively. These findings demonstrate the importance of renal parenchyma integrity for endocrine function of the kidney.

In Figures 5a and 5b, the distribution of complications according to CKD stages is shown to follow specific model. Patients from the CAKUT group showed the highest complication rate in end-stage CKD. In this group there was a significantly higher prevalence of bone mineral disorder and anemia (18.2% in both cases). In the group of patients with glomerular disease, most complications appear as early as stage 1 and are predominantly represented by dyslipidemia (73.7%) followed by hypertension (52.6%). The data coincide with those of other studies conducted so far, in which hypertension and dyslipidemia have been recorded in early stages of CKD. In a study conducted by Wong and colleagues, 63% of the 366 included patients were diagnosed with hypertension in stage 1 CKD [21]. The inverse correlation between impairment of kidney function, and occurrence of complications in CAKUT-CKD in the pediatric population, has been demonstrated in other studies such as those conducted by Chou et. al in Taiwan, Bek and colleagues in Turkey and the working group of Ardissino in Italy [20, 22, 23].

Short stature, as illustrated in Figure 6 showed the highest prevalence among end-stage CAKUT-CKD patients (22.7%), followed by stage 3 CAKUT-CKD patients (13.6%). One stage 4 glomerular disease - CKD patient representing 5.2%, had growth failure. This is supported by evidence from literature that attributes growth failure to a complex multifactorial ethiopathogeny. Metabolic acidosis, anemia and phospho-calcic metabolism disorders as well as human growth hormone (hGH) resistance in uremia contribute to a decreased height in CKD patients [7-9, 24].

Conclusions

1. Congenital anomalies of the kidney and the urinary Tract (CAKUT) represent the main cause for CKD in children.

2. Similar to adults, the most common complications of CKD in children are represented by dyslipidemia, hypertension, anemia and mineral and bone disorder.

3. There is a correlation between the etiology of CKD and the complications it causes. CAKUT are associated with anemia and mineral and bone disorder, whereas glomerular disease causes hypertension and dyslipidemia.

4. Glomerular disease associates complications at onset of CKD with normal or slightly decreased GFR values. CAKUT require longer until the onset of complications, in more advanced stages.

5. Short stature due to decreased bioavailability of somatotropin in uremia, metabolic acidosis, anemia and phospho-calcic metabolism disorders is specific for the pediatric population. A higher prevalence is noted in advanced stages of CKD.

6. Screening and early diagnosis of CKD and its complications, as well as close monitoring and appropriate therapy, are crucial to prevent disease progression and complications.

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Correspondence to:

Otilia Marginean
I. Nemoianu Street, no.2, 300011
Timisoara, Romania
e-mail: omarginean@ymail.com