CHRONIC KIDNEY DISEASE – PEDIATRIC RISK FACTORS

Velibor Tasic¹, Aleksandra Janchevska¹, Nora Emini¹, Emilija Sahpazova¹, Zoran Gucev¹, Momir Polenakovic²

¹ University Children's Hospital, Medical Facultu, Skopje, R. Macedonia

² Macedonian Academy of Sciences and Arts, Skopje, R. Macedonia

Corresponding Author: Prof. Velibor Tasic, MD, PhD, University Children's Hospital, Medical School Skopje, 17 Vodnjanska, 1000 Skopje, Macedonia, E-mail: vtasic2003@gmail.com

Abstract

The knowledge about the progression of chronic kidney disease is an important issue for every pediatric nephrologist and pediatrician in order to implement appropriate measures to prevent wasting of renal function and the final consequence – end stage renal disease with the need for the dialysis and transplantation. Therefore it is important to know, treat or ameliorate the standard risk factors such as hypertension, proteinuria, anemia, hyperparathyroidism etc. In this review devoted to the World Kidney Day 2016 we will pay attention to the low birth parameters, obesity, hyperuricemia and smoking which emerged as particularly important risk factors for children and adolescent with chronic kidney disease.

Keywords: chronic kidney disease, children, low birth parameters, smoking, obesity, hyperuricemia

Introduction

This review was produced for the World Kidney Day 2016 in order to attract the attention of health professionals to the pediatric aspects of the chronic kidney diseases [1]

The etiology of the chronic kidney disease (CKD) differs between pediatric and adult patients. Diabetic nephropathy, hypertension, and autosomal dominant polycystic kidney disease are prevalent diseases in adults, while in children the congenital anomalies of the kidney and urinary tract (CAKUT) is the most common pathology in 50%, followed by the hereditary nephropathies and the glomerulonephritis [2]. Cardiovascular events are the most common cause of death in pediatric CKD patients, with risk 1,000 times higher in the end stage renal disease (ESRD) population compared to the age-matched non-CKD population. Left ventricular hypertrophy, increased carotid

artery intima-media thickness and carotid arterial wall stiffness are early markers of the cardiovascular morbidity in this population. The coronary artery calcification which is a proven early marker of increased cardiovascular mortality in adults with CKD is also demonstrated in children with advanced CKD [3]. The disturbances in the mineral metabolism which are prominent in children also contribute to development of vascular calcification [4].

The standard factors which may affect the progression of CKD in adults are hypertension, proteinuria, glomerular etiology, male gender, anemia, diabetes, dyslipidemia, hyperparathyroidism, malnutrition (hypoalbuminemia) etc. These factors also operate in children. In children, the age is also an important risk factor; those < 2 years and pubertal children more frequently initiate renal replacement therapy. This is the result of the accelerated gro-

with at that age and the increase in the body mass which cannot be compensated with adequate renal function.

In this review we cannot analyze all these factors, but we will focus to those which attracted the attention of the researchers in the last two decades and which became global health problem, but could be modified or ameliorated by appropriate medical intervention and increased public awareness (low birth parameters, smoking, obesity and hyperuricemia).

Low birth parameters

In the last two decades the low birth parameters attracted the attention of many researchers since there is evidence that the adverse events in utero lead to impaired nephrogenesis and increase the risk of CKD later in life. There is a higher prevalence of children born with low birth parameters in cohorts of CKD patients compared with the subjects without CKD.

The abnormal birth history [prematurity, low birth weight (LBW), or small for gestational age (SGA)] is also associated with hypertension, cardiovascular morbidity, obesity and diabetes mellitus in adulthood. Each kilogram increase in birth weight, results in adult systolic blood pressure lower for 1–2 mmHg. [5, 6] The postnatal rapid weight gain is also associated with the increased risk for future cardiovascular morbidity [6, 7, 8]. It has not yet been defined what is the time required to see these effects because the pediatric studies revealed contradictory results [9]. A possible explanation for these conflicting results is the method of blood pressure measurement. It seems that 24-hour ambulatory blood pressure measurement (ABPM) is more sensitive than office blood pressure measurement to confirm this association.

Lurbe and co-workers performed ABPM in 630 healthy children, all of whom had been born at full term, by ABPM at a mean age of 9.9 years [10]. Although the strongest predictor of the current 24-hr systolic BP was the current weight, the birth weight had a significant inverse relationship on both 24-hour systolic BP and BP variability. Bayrakci et al investigated a group of 41 children born preterm (30 were small for gestational age) and their ABPM

compared with a group of children born at term [11]. The preterm group had higher nocturnal systolic BP, elevated nocturnal systolic and diastolic blood pressure loads, and blunted nocturnal dipping.

The researchers from the Chronic Kidney Disease in Children (CKiD) study investigated if a child's abnormal birth history, which included the following parameters (low birth weight, prematurity, SGA, or intensive care unit stay in the neonatal period) had influence on the height and weight in children with CKD [12]. During the four year period 586 children with mild to moderate CKD were enrolled from 48 pediatric nephrology centers across North America. All eligible children were aged 1 to 16 years and had a Schwartz-estimated GFR between 30 and 90 ml/min per 1.73 m². This study showed that LBW and SGA were associated with lower weight, especially in children with a glomerular etiology of CKD. Second, children with a history of LBW or SGA, regardless of the type of CKD diagnosis, were disproportionately short in stature. This study clearly proved that LBW and SGA are novel risk factors for abnormal growth in children with CKD.

In a combined study including the Pediatric Nephrology Departments at Hannover Medical School and Charite Hospital in Berlin perinatal data were analyzed in 435 children with CKD stages 3–5 of different etiology [13]. The patients were stratified in three groups [congenital n = 260 (60%), hereditary n = 93 (21%) and acquired n = 82 (19%) CKD etiology]. Low birth parameters (prematurity and SGA) were significantly more prevalent in the three groups compared with the referent population. The prevalence of prematurity/SGA expressed in % in the three groups were as follows: congenital (39.3% / 29.2%), hereditary (24.7% / 22.6%) and acquired CKD (15.5% / 29.3%); these percentages were significantly higher compared to 8% (for both) in the referent population. The authors concluded that both SGA and prematurity predispose for advanced renal disease in childhood and that fetal kidney disease impairs fetal growth. The practical implication from this study is that the acquired renal diseases may have different outco-

mes, those with low birth parameters have higher risk for CKD.

Low birth parameters are factor for initiation of CKD, but are not a significant factor for progression to ESRD, as it was shown in a large Japanese pediatric study [14].

Obesity

In the last two decades there is a global, worldwide epidemic of obesity affecting not only adults but particularly children and adolescents. The new style of life, lack of proper education and aggressive marketing of the junk food industry contributed to the magnitude of this epidemic. In the year 2008, 1.4 billion people worldwide were overweight, and 500 million were obese. The situation is alarming since in 2010, 40 million children under the age of 5 years were overweight or obese [15]. In parallel with these data there is an increasing prevalence of CKD in adults and children.

Obesity is co-morbidity associated with CKD, but vice versa, it can be a strong risk factor for CKD and its progression. It is well known that low birth parameters may be associated with the low nephron numbers and obesity and risk of CKD later in the life. Leptin and adiponectin are elevated in obese subjects and may be involved in pathogenesis and progression of CKD. Additional factors such as hypertension, increased cardiovascular morbidity, insulin resistance, dyslipidemia, and lipotoxicity, may play important roles in the pathogenesis of CKD in obesity [15–16].

It was shown that obesity is independent risk factor for progression of CKD as in the case of IgA nephropathy clinically and pathologically [17]. Worsening of the renal function is clearly demonstrated in patients with unilateral renal agenesis or nephrectomy. Also, the higher rate of renal allograft dysfunction was evidenced in kidneys from obese donors compared to lean donors' kidneys [18]. These results indicate that obesity initiates development and progression of CKD.

It is of note that decrease of the body weight and strong public awareness of obesity as a risk factor for CKD may result in decrease of its prevalence and general population health benefits.

Hyperuricemia

There is evidence that hyperuricemia increases the risk for cardiovascular mortality and morbidity, hypertension and CKD. In experimental models in rats it was shown that hyperuricemia leads to elevated blood pressure, proteinuria, renal dysfunction, and progressive renal and vascular disease. The principal effects of the serum levels of uric acid are endothelial dysfunction, activation of the local renin-angiotensin system, increased oxidative stress, and proinflammatory and proliferative actions [19]. A small number of short-term, single-center clinical studies support the beneficial influence of the pharmaceutical reduction of the serum uric acid on the total cardiovascular risk, as well as on the renal disease development and progression. Hyperuricemia is probably related to the incidence of primary hypertension in children and adolescents, as serum uric acid lowering by allopurinol has an antihypertensive action in this group of patients. Finally, it is clear that the adequately powered randomized controlled trials are urgently required to elucidate the role of uric acid in cardiovascular events and outcomes, as well as in the development and progression of CKD.

Noone and Marks investigated the prevalence of hyperuricemia in a pediatric chronic kidney disease clinic [20]. 116 children (age 0.4–16 years) were enrolled in the study. The prevalence of hyperuricemia in those with an eGFR < 60 mL/min/1.73 m² was 70%. This study showed that hyperuricemia was significantly associated with increased body mass index, albuminuria, renal dysfunction with reduced eGFR, and hypertension.

The researchers from the CKiD Cohort study investigated the role of hyperuricemia in progression of CKD in children and adolescents [21]. The following parameters were investigated: age, sex, race, blood pressure status, GFR, CKD cause, urine protein-creatinine ratio (< 0.5, 0.5 – < 2.0, and ≥ 2.0 mg/mg), age- and sex-specific body mass index > 95th percentile, use of diuretics, and serum uric acid level. The study revealed that older age, male sex, lower GFR, and body mass index > 95th percentile were associated with higher uric acid levels. Participants with uric acid levels of 5.5 to 7.5 or > 7.5 mg/dL had 17% or 38% shorter time to

decrease the GFR by 30% or initiation of renal replacement therapy respectively.

Smoking

It is well known that smoking is one of the strongest factors for cardiovascular mortality and morbidity in adults. Smoking is associated with albuminuria, progressive renal insufficiency and graft loss. Second hand smoking (SHS) is underrated pathogenic factor and in children it is associated with blood pressure variability, elevated C reactive protein and poorer neurocognitive functions. The Midwest Pediatric Nephrology Consortium investigated cigarette smoking and second-hand smoking exposure in adolescents with chronic kidney disease [22]. The urinary cotinine/creatinine level was investigated and was found to be higher in those who lived with a smoker or had a friend smoker.

Another American study investigated smoking and second hand smoking [23]. According to the urinary cotinine levels, 22% of the subjects were exposed to SHS. There was a significant correlation between the SHS and the lower maternal education, the African American race, the greater prevalence of the nephrotic range proteinuria and the left ventricular hypertrophy.

Hogan et al. showed that albuminuria was associated with cigarette smoking independent of other comorbidities, such as hypertension and diabetes [24]. Garcia-Esquinas et al. demonstrated a linear reduction in the estimated glomerular filtration rate (eGFR) with rising serum cotinine levels among the healthy adolescents who were active smokers [25]. There are adult studies which proved the effect of tobacco use in patients with IgA nephropathy, diabetic nephropathy and allograft nephropathy [26]. In humans, nicotine, the active ingredient in tobacco, promotes mesangial cell proliferation and extracellular matrix production via recently discovered nicotinic receptors in the mesangial cells. Besides nicotine there are > 4000 toxic chemicals including carbon monoxide, arsenic, vinyl chloride, cadmium, lead, and acrolein [26]. Lead is well known nephrotoxin and is associated with the CKD progression. Acrolein has been shown to induce apoptosis of renal cells and generation of

reactive oxygen species. Other mechanisms by which smoking may contribute to proteinuria and CKD progression are induction of hypoxia, intrarenal vasoconstriction and stimulation of proinflammatory cytokines.

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Резиме

ХРОНИЧНА БУБРЕЖНА БОЛЕСТ – ПЕДИЈАТРИСКИ РИЗИК-ФАКТОРИ

**Велибор Тасиќ¹, Александра Анчевска¹,
Нора Емини¹, Емилија Шахпазова¹,
Зоран Гучев, Момир Поленаковиќ²**

¹ Универзитетска клиника за детски болести, Медицински факултет, Скопје, Р. Македонија

² Македонска академија на науките и уметностите, Скопје, Р. Македонија

Знаењето за прогресијата на хроничната бубрежна болест е од големо значење за секој педијатриски нефролог и педијатар заради имплементирање соодветни мерки за превенирање на губење на бубрежната функција и крајна последица терминална уремија со потреба од дијализа и трансплантација. Затоа е потребно да се познаваат, третираат и ублажат стандардните ризик-фактори, како што се хипертензија, протеинурија, анемија, хиперпаратиреоидизам и други. Во овој ревијален труд посветен на Светскиот ден на бубрегот 2016, особено внимание посветуваме на ниските родилни параметри, дебелината, хиперурикемијата и пушењето, кои се наметнаа како особено важни ризик-фактори кај деца и адолесценти со хронична бубрежна болест.

Клучни зборови: хронична бубрежна болест, ниски родилни параметри, пушење, дебелина, хиперурикемија