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DIAGNOSTIC VALUE OF URINARY BIOMARKERS IN CHRONIC KIDNEY DISEASES AT CHILDREN

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Abstract

Chronic kidney disease(CKD) typically develops as a consequence of gradually advancing kidney ailments, and it rarely sees complete reversibility. The aim of the study is to evaluate the value of urinary biomarkers in children with progression of chronic kidney disease.

The is a retrospective-prospective study in which includes 95 pediatric patients with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD. The patients are aged 0 to 14 years who came to the University Clinic for Children's Diseases-Skopje at the nephrology department and the subspecialist nephrology outpatient clinic, in period from January 2019 to June 2022.

The study group is divided into three groups, study group 1, which includes 41/95 pediatric patients(43.16%)with congenital anomalies of the kidneys and urinary tract, study group 2, which includes 34/95 pediatric patients(35.79%)with tubulopathies and metabolic disorders with renal affection and study group three which includes20/95(21.05%)pediatric patients with other nephrological-urological diseases. In our study, CKD is more prevalent in males 64 (67.37%) while 31 (32.63%) are females, according to age, patients aged 5-14 years (57.3 %). The average values of urine NGAL(ng/ml), β2-Microglobulin and albuminirua showed that there is a significant difference in relation to this parameter in three groups of pediatric patients at the first examination ($p<0.05$).

As the landscape of CKD continues to reveal novel insights into its intricate mechanisms, urine biomarkers will continue to assume a pivotal role in furthering our comprehension of the disease and shaping the trajectory of personalized medicine for CKD children.

Key words: chronic kidney disease (CKD), urine biomarkers, NGAL (Neutrophil Gelatinase-Associated Lipocalin).

Introduction

Despite significant progress in diagnosis and therapy over the last decade, evaluating renal failure remains difficult. Chronic kidney disease (CKD) typically develops as a consequence of gradually advancing kidney ailments, and it rarely sees complete reversibility [1].

This condition is often linked to childhood cases involving obstructive uropathy, congenital issues like aplastic, hypoplastic, or dysplastic kidneys, as well as various other underlying factors. In CKD, nearly all bodily systems are eventually affected and compromised [2].

Childhood CKD presents unique clinical characteristics, particularly those significantly impacting growth. Furthermore, some paediatric CKD features, such as its causes and cardiovascular complications, represent variables that not only influence a child's health but also shape the life of the adult they will become. This lasting impact is often underestimated but should not be overlooked. Additionally, CKD carries substantial psychosocial consequences, affecting both patients and their families [3].

Parents not only assume their parental roles but also take on responsibilities typically associated with nurses and doctors. Thus, it is crucial to recognize that the improved clinical and therapeutic management of paediatric CKD, resulting in increased patient survival, will give rise to a considerable number of affected adults confronting CKD-related issues that began in childhood. Moreover, CKD in children exhibits unique features and challenges distinct from those faced by adult patients. This makes paediatric CKD a distinct clinical entity [4].

As per the KDIGO guidelines, chronic kidney disease (CKD) is characterized by kidney damage, either in structure or function, or a decline in glomerular filtration rate (GFR) persisting below 60 mL/min/1.73 m² of body surface area for more than three months [5-7].

Consequently, CKD defines renal dysfunction as a continuous spectrum, rather than a sudden change in renal function, both in children and adults. This characteristic makes studying the epidemiology of CKD a challenging task. Furthermore, epidemiological data regarding CKD may underestimate its true incidence and prevalence since CKD often lacks clinical symptoms, particularly in its early stages.This challenge partly stems from the historical absence of a universally accepted CKD definition and a clearly defined severity classification. However, recent efforts, including the introduction of the KDIGO guidelines, have partially addressed this issue [8-9].

Due to these complexities, most studies tend to account for patients with moderate to severe CKD or end-stage renal disease (ESRD), and they are not typically population-based.16,17 Moreover, registries for childhood CKD often have limited reach, focusing on smaller reference populations.18 Despite these limitations, the reported incidence of paediatric CKD in Europe hovers around 11–12 cases per million of the age-related population (pmarp) for stages 3–5, with a prevalence of approximately 55–60 pmarp.There five stages of Chronic Renal Disease [10-14].

The initial stage of chronic renal disease corresponds to a Glomerular Filtration Rate (GFR) ranging under 90% of the normal rate for an individual's age. Importantly, this stage is typically asymptomatic.

Mild renal failure – GF is reduced to 60-89% of normal values. Serum creatinine is slightly elevated, the patient has no symptoms of CKD. It is necessary to diagnose the underlying disease and treat it if possible.

The subsequent stage of chronic renal disease is often referred to as chronic renal insufficiency. In this stage, the GFR typically falls within the range of 30% to 59% of the normal rate for a person's age. It's common to observe substantial proteinuria exceeding 1,000 mg/d, yet patients often remain asymptomatic. Hyposthenuria (reduced ability to concentrate urine) and nocturia (increased nighttime urination) are characteristic features of this stage.

It's worth noting that while conditions like infection and dehydration rarely cause significant issues in the initial stage due to a broader margin of renal functional reserve, they can lead to severe azotemia (an excess of nitrogenous waste in the blood) in the second stage.

The four stage of chronic renal disease, often referred to as CRF, is characterized by a Glomerular Filtration Rate (GFR) ranging from 15% to 29% of the normal rate. At this stage, clinical features become more evident and include anemia, acidosis, hyperphosphatemia, hypocalcemia, as well as renal osteodystrophy and rickets.

The five and final stage of chronic renal disease is known as end-stage renal disease. It occurs when the GFR falls below 15% of normal. At this advanced stage, severe neurological, cardiovascular, gastrointestinal, hematological, and skeletal abnormalities become prominent. Consequently, preparations for initiating dialysis or transplantation must commence as the child transitions into this end-stage of the disease.

It's worth noting that while the first three stages of CRF have distinct characteristics, the features of the last two stages tend to overlap [15-18].

Paediatric nephrologists should recognize that complications arising from childhood CKD extend well beyond childhood and influence the outcomes of young adults with CKD. Conversely, nephrologists caring for young adults with CKD or adults who experienced CKD during childhood should grasp the unique characteristics of CKD in children, particularly its causes, to enhance their patients' care. In essence, nephrologists, whether tending to children or adults with CKD, must adopt a comprehensive perspective of their patients: one that looks to the future for the former and reflects on the past for the latter.Timely identification and effective management of CKD are imperative to prevent its advancement to end-stage renal disease (ESRD) or kidney failure. In this context, urine biomarkers have emerged as indispensable tools for diagnosing, monitoring, and foreseeing the prognosis of CKD. These biomarkers offer valuable insights into the progression of the disease and potential intervention strategies [19-22].

This article delves into the significance of urine biomarkers in the context of CKD, casting light on their pivotal role in enhancing patient outcomes and advancing the landscape of medical research. Understanding CKD and the Current Diagnostic Landscape: Often referred to as a "silent

epidemic," CKD often remains asymptomatic during its early stages. Traditional diagnostic methods like serum creatinine and estimated glomerular filtration rate (eGFR) possess limitations in effectively detecting CKD in its initial phases. By the time these markers exhibit significant alterations, a considerable portion of kidney function might already be compromised. This underscores the pressing need for diagnostic tools that are more sensitive and specific, enabling the identification of CKD at an earlier juncture [23-24].

Promising Several urine biomarkers have exhibited promise in both CKD research and clinical practice:

1. Albuminuria: Elevated ACR levels are indicative of kidney damage and are frequently employed to detect and monitor CKD [25].
2. NGAL (Neutrophil Gelatinase-Associated Lipocalin): serves as an early indicator of kidney injury and inflammation, offering insights into both acute kidney injury and CKD progression [26].
3.β2-Microglobulin (B2M): is a protein that is eliminated almost exclusively by the kidneys, predominantly by glomerular filtration but possibly also by some direct uptake from the blood. an can be used as a potential marker to identify patients at risk of progression [27].

The aim of the study is to evaluate the value of urinary biomarkers in children with progression of chronic kidney disease.

Material and methods

The study was conducted at University Clinic for Children's Diseases-Skopje. It is a retrospective-prospective study, in which 95 patients in the period from 01.01.2019 to 31.12.2022.

Inclusion criteria for inclusion in the study are:

- confirmed chronic kidney disease according to the above parameters,
- appropriate medical documentation, laboratory analysis results and imaging studies
- informed consent for inclusion in the study

Exclusion criteria:

- incomplete medical documentation, lack of a set of laboratory tests and technically inadequate imaging studies (which cannot be interpreted)
- not receiving informed consent to participate in the study

The examined group will be divided into three groups:

Group I included pediatric patients with congenital anomalies of the kidneys and urinary tract,

Group II included pediatric patients with tubulopathies and metabolic diseases with renal affection,

Group III included pediatric patients with other nephrological-urological diseases.

The three groups will be compared with each other regarding the degree of chronic kidney disease, the values of urinary NGAL, urinary beta 2 microglobulin, microalbumin in urine. In the preparation of this study, we used the data from the electronic system for outpatient examinations and the history of the disease.

The laboratory analyzes were performed at the Department of Clinical Laboratory (hematology, biochemistry, immunology, allergology) at the University Clinic for Children's Diseases-Skopje.

When examining the serum and urine of patients with chronic kidney disease, we used the following methods: for NGAL in urine Chemiflex (Abbott Architect i 1000 sr) ng /ml, for beta 2 microglobulin in urine ELFA (Vidas PC blue) mg/L, for microalbumin in urine EACLIA (Immulite 200 Siemens) ug/ mL.

Statistical analysis was done with SPSS software for Windows version 26. Categorical variables between the three groups were compared with Chi-square test (X^2), while for low frequencies with Fisherexact test. The value of $p<0.05$ was taken as a statistically significant difference.

Results

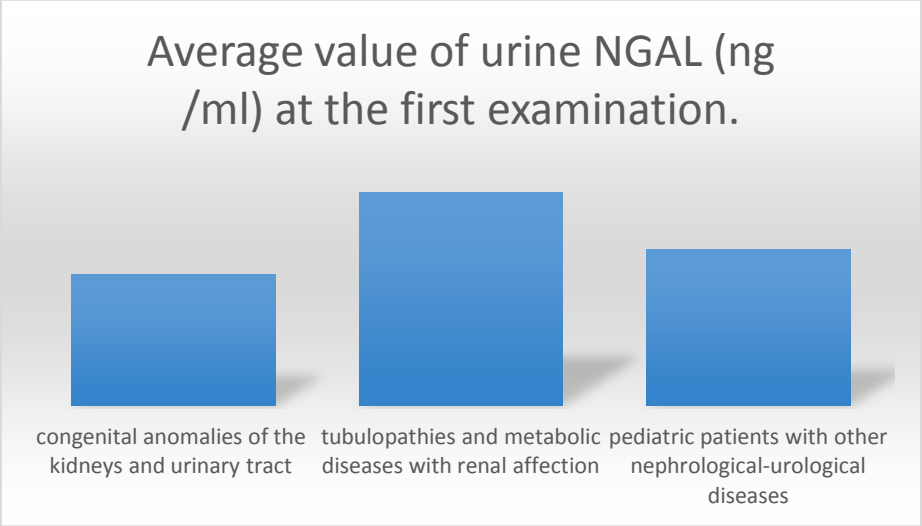
The study includes 95 pediatric patients with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD. The patients are aged 0 to 14 years who came to the University Clinic

for Children's Diseases-Skopje at the nephrology department and the subspecialist nephrology outpatient clinic, in period from January 2019 to June 2022.

The study group is divided into three groups, study group 1, which includes 41/95 pediatric patients (43.16%) with congenital anomalies of the kidneys and urinary tract, study group 2, which includes 34/95 pediatric patients (35.79%) with tubulopathies and metabolic disorders with renal affection and study group three which includes 20/95 (21.05%) pediatric patients with other nephrological-urological diseases.

According to gender, the male gender dominated in pediatric patients with congenital anomalies of kidneys and urinary tract 27/41 (65.85%), in pediatric patients with tubulopathies and metabolic diseases with renal affection 25/34 (73.53%) and in pediatric patients with other nephrological-urological diseases 12/20 (60 %). There is a statistically significant difference between gender in terms of CKD in the studied groups $p < 0.05$. According to age, there is no significant difference regarding this parameter in the three studied groups $p<0,01$.

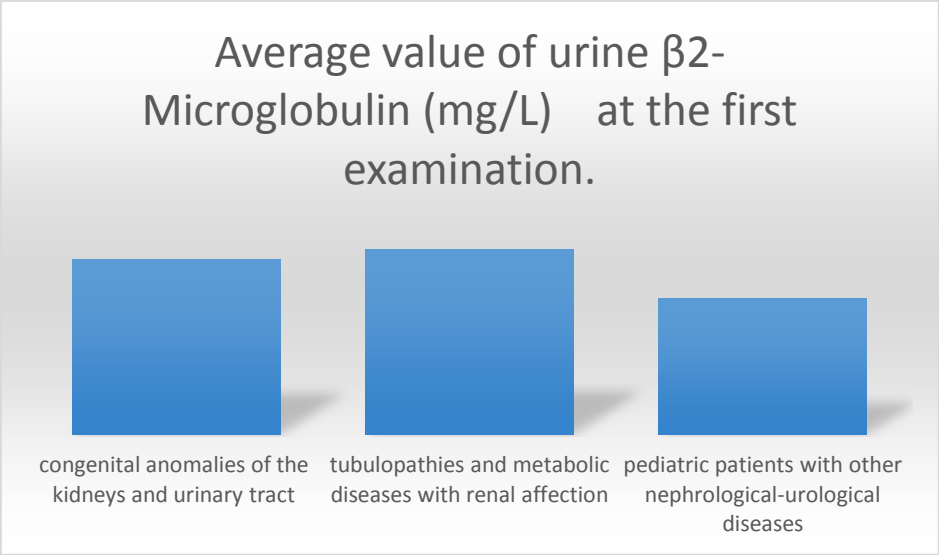
Chart number 1. Distribution of pediatric patients with congenital anomalies of the kidneys and urinary tract, tubulopathies and metabolic diseases with renal affection and pediatric patients with other nephrological-urological diseases according to the average value of urine NGAL (ng /ml) at the first examination.



The average values of urine NGAL (ng /ml) showed that there is a significant difference in relation to this parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 195 ±1.55 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 317±1.17 and pediatric patients with other nephrological-urological diseases 233±1.23 at the first examination $p<0.05$.

The average values of urine NGAL (ng /ml) showed that there is no significant difference regarding this parameter in pediatric patients with congenital anomalies of kidneys and urinary tract 81±1.25 in relation to pediatric patients with tubulopathies, metabolic diseases with renal affection 97±1.37 and pediatric patients with other nephrological-urological diseases 89±1.15 at control examination $p<0.01$.

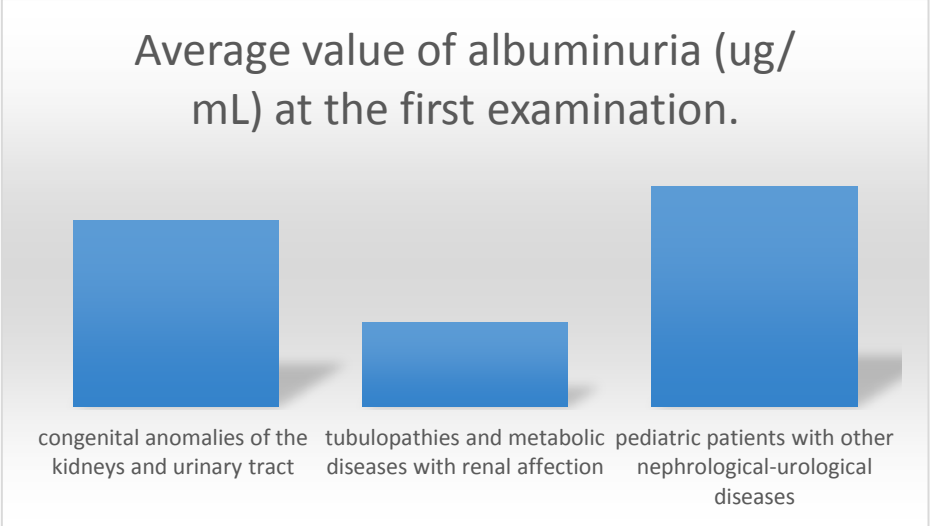
Chart number 2. Distribution of pediatric patients with congenital anomalies of the kidneys and urinary tract and tubulopathies and metabolic diseases with renal affection according to the average value of urine β2-Microglobulin (mg/L) at the first examination.



The average values of β2-Microglobulin (mg/L) showed that there is a significant difference in relation to this parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 3.2 ±1.72 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 2,9±2.1 and pediatric patients with other nephrological-urological diseases 1,3±1.15 at the first examination $p<0.05$.

The average values of urine β2-Microglobulin (mg/L) showed that there is no significant difference regarding this parameter in pediatric patients with congenital anomalies of kidneys and urinary tract 0.13±1.23 in relation to pediatric patients with tubulopathies, metabolic diseases with renal affection 0.11±1.12 and pediatric patients with other nephrological-urological diseases 0.09±1.12 at control examination $p<0.01$.

Chart number 3. Distribution of pediatric patients with congenital anomalies of the kidneys and urinary tract and tubulopathies and metabolic diseases with renal affection according to the average value of albuminuria (ug/ mL) at the first examination.



The average values of albuminuria (ug/ mL) showed that there is a significant difference in relation to this parameter in pediatric patients with congenital anomalies of the kidneys and urinary tract 53 ±1.12 in relation to pediatric patients with tubulopathies and metabolic diseases with renal affection 35±1.15 and pediatric patients with other nephrological-urological diseases 59±1.15 at the first examination $p<0.05$.

The average values of urine albuminuria (ug/mL) showed that there is no significant difference regarding this parameter in pediatric patients with congenital anomalies of kidneys and urinary tract 26±1.12 in relation to pediatric patients with tubulopathies, metabolic diseases with renal affection 22±1.23 and pediatric patients with other nephrological-urological diseases 28±1.11 at control examination $p<0.01$.

Discussion

This study presents a retrospective-prospective study, which includes pediatric patients with clinical signs, symptoms, laboratory analyses, and imaging studies for CKD. The patients are aged 0 to 14 years who came to the University Clinic for Children's Diseases-Skopje in the nephrology department. and a subspecialty outpatient clinic for nephrology, in the period from January 2019 to June 2022.

The study processed data on 95 pediatric patients with CKD and that 41/95 pediatric patients (43.16%) with congenital anomalies of the kidneys and urinary tract, 34/95 pediatric patients (35.79%) with tubulopathies and metabolic disorders with renal affection and 20/95 (21.05%) pediatric patients with other nephrological-urological diseases.

In our study, CKD is more prevalent in males 64 (67.37%) while 31 (32.63%) are females, which correlates with the data from the published study by Francesca Becherucci [28]. According to age, patients aged 5-14 years (57.3 %). The average values of urine NGAL(ng/ml), β2-Microglobulin and albuminirua showed that there is a significant difference in relation to this parameter in three groups of pediatric patients at the first examination $p<0.05$. The average values of urine NGAL(ng/ml), β2-Microglobulin and albuminirua showed that there is no significant difference regarding this parameter in three groups of pediatric patients at control examination $p<0.01$.Chronic kidney disease (CKD) can be deceptively subtle in children. While it's relatively rare among the paediatric population, CKD can have profound and enduring consequences. Shockingly, the mortality rate for children with End-Stage Renal Disease (ESRD) undergoing dialysis therapy is 30–150 times higher than that of the general paediatric population. Furthermore, the life expectancy of a child on dialysis is approximately 50 years less than that of a healthy child [29-31].

Kidney transplantation offers a significant improvement in prognosis and stands as the best therapeutic option for children with ESRD. Nevertheless, most complications associated with this clinical condition impact the patient's health long before kidney function is irrevocably lost, even when it remains stable over time with conservative therapy [32].

Urine Biomarkers: Revealing Concealed Insights: Intriguingly, urine, typically regarded as a waste product, conceals a wealth of information regarding kidney health. Urine biomarkers encompass substances or molecules quantifiable within urine samples, which reflect diverse facets of kidney function and overall health. Unlike serum biomarkers, urine biomarkers hold distinctive advantages, as they directly mirror the renal microenvironment and offer insights into the ongoing pathological mechanisms within the kidney [33-40].

Key Role of Urine Biomarkers in CKD: are early detection of CKD in its early stages, thereby facilitating timely interventions and initiating suitable management strategies, prognosis and risk evaluation of CKD and the like lihood of unfavorable outcomes, such as cardiovascular events, urine biomarkers can effectively trace the decline in kidney function and the gravity of kidney damage.

These biomarkers offer valuable insights into the progression of the disease and potential intervention strategies. This study delves into the significance of urine biomarkers in the context of CKD, casting light on their pivotal role in enhancing patient outcomes and advancing the landscape of medical research.

Conclusion

This study on chronic kidney disease answered the question that was formulated as the aim of the research. The importance of urine biomarkers in the realms of CKD diagnosis, monitoring, and prognosis stands as an undeniable facet. These biomarkers delve deep into kidney health and disease advancement, permitting early interventions, customized treatment strategies, and enhanced patient outcomes. As the landscape of CKD continues to reveal novel insights into its intricate mechanisms, urine biomarkers will continue to assume a pivotal role in furthering our comprehension of the disease and shaping the trajectory of personalized medicine for CKD children.

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