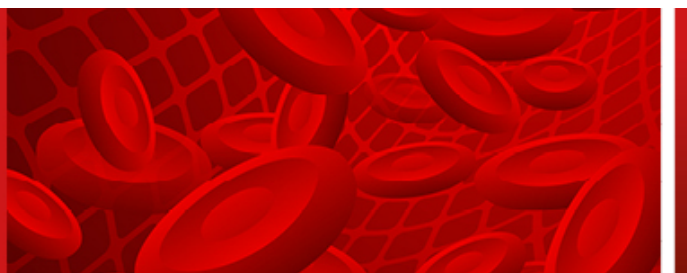


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## **Is urinary type IV collagen a good marker of early impairment of renal function in childhood cancer survivors?**

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### **Abstract**

**Introduction:** Nephrotoxicity, as a side effect of antineoplastic treatment, can occur in childhood cancer survivors (CCSs). It worsens their quality of life especially if it leads to chronic kidney disease (CKD). Collagen turnover is known to be disturbed in CKD. Urinary type IV collagen (U-Col4) is recognized as an exponent of extracellular matrix synthesis and degradation in glomeruli and is thus involved in this turnover. The purpose of this study was to evaluate the usefulness of U-Col4 in assessing early renal impairment in CCSs.

**Material and methods:** Seventy-eight CCSs, without CKD, bilateral kidney tumors, congenital kidney defects, urinary tract infections and diabetes, at least one year after ending antineoplastic treatment, and aged 1–18 years, were divided into three groups: 1) patients after nephroblastoma treatment (n = 18); 2) patients after other solid tumors treatment (n = 42); and 3) patients after anti-hematopoietic and lymphatic system proliferative treatment (n = 18). Concentrations of creatinine and cystatin C in serum, and of albumin, creatinine, N-acetyl- $\beta$ -D-glucosaminidase (NAG), and U-Col4 in urine, were measured, and a general urine analysis was performed. The albumin-creatinine ratio (ACR), the urine U-Col4/creatinine ratio, the

urine NAG/creatinine ratio and the estimated glomerular filtration rate were calculated according to the Schwartz equation and the Filler equation.

**Results:** We did not find any differences between the groups in the evaluated biochemical parameters. Weak negative correlations were found between U-Col4 and urine NAG/creatinine ratio ( $p = 0.02$ ,  $R = -0.27$ ) and ACR ( $p = 0.00$ ,  $R = -0.39$ ).

**Conclusions:** Evaluation of the usefulness of U-Col4 in assessing early renal impairment in CCSs requires further study. CCSs should be monitored for potential complications of antineoplastic treatment, even many years after its completion.

**Key words:** leukemia, solid tumors, survivors, late effects, nephrotoxicity, collagen type IV

## Introduction

Due to recent improvements in pediatric cancer treatment, the necessity of monitoring the long-term sequelae of antineoplastic treatment has become increasingly important.

Nephrotoxicity is one of the most common late sequelae of oncological treatment: based on meta-analyses performed by Kooijmans et al. [1], its prevalence can be up to 80%. According to Krawczuk-Rybak et al.'s study [2] concerning the health status of Polish childhood cancer survivors (CCSs), urinary system toxicities increase with longer the follow-up (FUP) time — from 19.2% (FUP <2 years) to 23.0% (FUP 2–4 years), 32.7% (FUP 5–10 years), 34.9% (FUP 11–15 years), and 47.6% (FUP >15 years).

The pathomechanism of renal injury in pediatric oncological patients depends on the kind of disease including the cancer itself (tumor infiltration, urinary tract obstruction etc.), diagnostic procedures, multimodal therapy including chemotherapy (e.g. cisplatin, carboplatin, ifosfamide), radiotherapy, immunotherapy, surgery (e.g. nephrectomy), and supportive treatment [3]. In addition, deviations in antineoplastic treatment implementation are associated with an increased risk of death or relapse [4].

All of the factors mentioned above, alone or together, can cause glomerular filtration rate (GFR) impairment, tubulopathy, and hypertension [1]. Glomerular hyperfiltration is well documented as a long-term consequence of nephrectomy [5–8].

In turn, case reports in CCSs have described proteinuria, hypertension and progressive chronic kidney disease (CKD) due to focal glomerulosclerosis, most likely as a consequence of hyperfiltration [9–11].

The complicated and varied pathomechanisms of nephrotoxicity require new markers to reflect the changes taking place in the kidneys, and are thus useful in clinical assessment. Over the last two decades, many markers have been tested to find the most sensitive and specific indicators of drug-induced nephrotoxicity [12]. One of these is urinary type IV collagen (U-Col4) — the main component of the glomerular basement membrane (GBM) and the extracellular matrix (ECM) [13]. Loss of balance between ECM protein synthesis and degradation in CKD leads to fibrosis, and is associated with changes in collagen turnover processes. There are studies showing that subgroups of patients, differing in terms of the severity and course of CKD, can be identified based on these disturbances [14]. The best evidence that U-Col4 is a good marker of CKD comes from patients with diabetes. Together with albumin excretion, U-Col4 is used to monitor the development and progression of diabetic nephropathy, especially in type 2 diabetes [15–17]. It is also recognized as a good marker of CKD progression in the course of hypertension [18].

The aim of this study was to evaluate the excretion of U-Col4 and established parameters of kidney function and to determine its usefulness as a marker of early renal impairment in CCSs.

## **Material and methods**

### ***Characteristics of patients***

Seventy-eight CCSs were included in the study. All of these children were patients of the Department of Pediatrics, Hematology and Oncology, Medical University of Gdansk, Poland. The inclusion criteria of the study were: age <18 years and a minimum of one year after antineoplastic treatment. The exclusion criteria were: age <1 year, CKD, bilateral kidney tumors, congenital kidney defects, urinary tract infections, diabetes and pregnancy.

The study population was aged between 17 and 215 months, with a median age and IQR of 133.5 (71.0÷173.0) months. There were 45 boys and 33 girls (58% and 42%). The study population was divided into three groups: Group 1 — patients after nephroblastoma treatment (n = 18); Group 2 — patients after other solid tumor treatment (n = 42, neuroblastomas — 19, rhabdomyosarcomas — 8, hepatoblastomas — 6, brain tumors — 4, germ cell tumors — 3, osteosarcoma — 1, Ewing's sarcoma — 1); and Group 3 — patients after anti-hematopoietic and lymphatic system proliferative treatment (n = 18). During a routine visit to the department, a medical history was taken, and physical examinations with measurements of body mass, height, and blood pressure as well as laboratory tests were performed. The albumin-creatinine ratio (ACR), urine U-Col4/creatinine ratio, urine acetyl-β-

D-glucosaminidase (NAG)/creatinine ratio, and estimated glomerular filtration rate (eGFR) were calculated according to the Schwartz equation and the Filler equation.

### ***Blood pressure measurements***

Blood pressure (BP) was measured three times by means of the oscillometric technique. The average values of systolic and diastolic pressure were calculated and compared against the reference standards for age, sex, and height. The following were used as reference standards: for children aged 1–6.5 years, the Age-based Pediatric Blood Pressure Reference Charts of Baylor College of Medicine; and for children >6.5 years, the OLAF calculator of The Children’s Memorial Health Institute.

### ***Laboratory tests***

The measurements were performed by the Central Clinical Laboratory of the University Clinical Centre in Gdansk and the Department of Clinical Nutrition, Medical University of Gdansk. Concentrations of creatinine (creatinine<sub>s</sub>), and cystatin C (cystatin<sub>s</sub>) were measured in a single blood sample, and creatinine (creatinine<sub>u</sub>), albumin (albumin<sub>u</sub>), NAG and U-Col4 were measured in a single urine sample. Urine analysis was also performed. Creatinine<sub>s</sub> and creatinine<sub>u</sub> were assessed with the immunoenzymatic method (Abbott Laboratories, Warsaw, Poland), cystatin<sub>s</sub> with the immunonephelometric method (Siemens Healthcare, Warsaw, Poland), albumin<sub>u</sub> with the turbidimetric method (Abbott Laboratories, Warsaw, Poland) and U-Col4 with the immunoenzymatic method (Uscn Life Science Inc., Wuhan, China).

### ***Equations***

$$eGFR_{Sch} = 41.3 \times \left( \frac{H}{creatinine_s} \right)$$

$$\log GFR_F = 1.962 + \left[ 1.123 \times \log \left( \frac{1}{cystatin_s} \right) \right]$$

$$ACR = \frac{albumin_u}{creatinine_u \times 0.01}$$

where:  $eGFR$  — estimated glomerular filtration rate [ml/min/1.73 m<sup>2</sup>];  $H$  — height [m];  $creatinine_s$  — serum creatinine level [mg/dL];  $cystatin_s$  — serum cystatin C level [mg/L];  $ACR$  — albumin-creatinine ratio;  $albumin_u$  — urine albumin level [mg/dL];  $creatinine_u$  — urine creatinine level [mg/dL].

### **Statistical analyses**

The obtained results were analysed statistically. A normal distribution of the data was verified with the Shapiro-Wilk test. Parameters are presented as the median value and interquartile range (IQR). A non-parametric Kruskal-Wallis test was performed to compare groups. A correlation analysis was performed using Spearman's method. The level of significance was considered to be  $p < 0.05$ . Statistical analysis was performed using Dell Statistica software (Dell Inc.), version 13.

### **Ethics Committee**

This study was approved by the Independent Bioethical Committee of Scientific Researchers at the Medical University of Gdansk (NKBBN/417/2014-28 October 2014). Written informed consent was obtained from the legal guardians of the children and from those aged over 16 years.

### **Results**

The groups were similar in terms of age, sex, time at which treatment ended, body mass, height, systolic and diastolic blood pressure (SBP, DBP). The median time after the end of the anti-neoplastic treatment was 51.5 months in Group 1, 57.0 months in Group 2, and 39.0 months in Group 3. None of the studied patients met the clinical and laboratory criteria for a CKD diagnosis. The exact characteristics of the groups are set out in Table I. The assessment of BP is presented in Table II. Table III shows the values of the renal parameters obtained in each of the studied groups.

**Table I.** Age, time from end of treatment, body weight in study groups

<b>Characteristics</b>	<b>Group 1*</b>	<b>Group 2**</b>	<b>Group 3***</b>	<b><i>p</i> value</b>
Age [months]	115.5 (94.0÷173.0)	126.0 (70.0÷173.0)	153.0 (80.0÷172.0)	0.50
Time from end	51.5	57.0	39.0	0.13

of treatment [months]	(24.0÷135.0)	(26.0÷86.0)	(14.0÷53.0)	
Body mass [percentile]	46.0 (15.3÷74.0)	61.0 (23.0÷87.0)	55.5 (22.0÷85.0)	0.64
Height [percentile]	53.0 (29.0÷86.0)	45.0 (20.0÷79.0)	51.5 (32.0÷69.0)	0.80

\*Patients after nephroblastoma treatment; \*\*patients after other solid tumors treatment;

\*\*\*patients after anti-hematopoietic and lymphatic system proliferative treatment

**Table II.** Blood pressure (BP) in study groups

BP	Group 1*	Group 2**	Group 3***	p value
SBP [percentile]	64.5 (34.0÷93.0)	60.0 (38.0÷81.0)	63.0 (32.0÷95.0)	0.89
DBP [percentile]	89.5 (55.0÷97.0)	81.0 (60.0÷91.0)	74.0 (63.0÷85.0)	0.55

\*Patients after nephroblastoma treatment; \*\*patients after other solid tumors treatment;

\*\*\*patients after anti-hematopoietic and lymphatic system proliferative treatment; SBP — systolic blood pressure; DBP — diastolic blood pressure

**Table III.** Renal assessment in study groups

Renal function parameter	Group 1*	Group 2**	Group 3***	p value
Creatinine <sub>s</sub> [mg/dL]	0.6 (0.5÷0.8)	0.6 (0.4÷0.7)	0.5 (0.4÷0.7)	0.53
Cystatin <sub>s</sub> [mg/L]	0.79 (0.8÷0.9)	0.8 (0.7÷0.9)	0.8 (0.7÷0.8)	0.12
eGFR <sub>Sch</sub> [ml/min/1.73 m <sup>2</sup> ]	95.1 (86.4÷104.7)	101.6 (87.4÷119.2)	116.2 (96.8÷126.9)	0.07
eGFR <sub>F</sub> [ml/min/1,73 m <sup>2</sup> ]	119.4 (110.0÷124.7)	116.9 (103.1- 139.0)	126.6 (119.4÷148.3)	0.12
Albumin <sub>u</sub> [mg/L]	8.2 (5.6÷24.5)	12.4 (5.8÷24.2)	14.7 (10.6÷22.0)	0.68
Creatinine <sub>u</sub> [mg/dL]	74.6 (56.0÷108.6)	68.2 (43.4÷104.9)	75.6 (64.0÷144.4)	0.57
ACR [mg/g creatinine <sub>u</sub> ]	16.4 (9.9÷21.9)	16.4 (11.1÷46.2)	17.4 (8.4÷34.4)	0.76
NAG/creatinine <sub>u</sub> ratio [IU/g]	3.1 (2.3÷5.9)	5.4 (2.9÷9.5)	4.6 (2.0÷6.9)	0.13
U-Col4 [ng/mL]	10.2 (5.4÷21.3)	11.6 (7.4÷20.3)	13.3 (8.6÷15.9)	0.75
U-Col4/creatinine <sub>u</sub> ratio [ng/mg]	14.2 (8.8÷27.6)	16.1 (10.5÷34.9)	18.8 (9.5÷31.4)	0.62

\*Patients after nephroblastoma treatment; \*\*patients after other solid tumors treatment; \*\*\*patients after anti-hematopoietic and lymphatic system proliferative treatment; creatinine<sub>s</sub> — serum creatinine level; cystatin<sub>s</sub> — serum cystatin C level; eGFR<sub>Sch</sub> — estimated glomerular filtration rate by Schwartz equation; eGFR<sub>F</sub> — estimated glomerular filtration rate by Filler equation; ACR — albumin-creatinine ratio; albumin<sub>u</sub> — urine albumin level; creatinine<sub>u</sub> — urine creatinine level; NAG — N-acetyl-β-D-glucosaminidase; U-Col4 — urinary type IV collagen

There were no statistically significant differences in the concentrations of U-Col4 or the U-Col4/creatinine<sub>u</sub> ratio between the groups. There were no statistically significant differences in creatinine<sub>s</sub>, cystatin<sub>s</sub>, albumin<sub>u</sub>, creatinine<sub>u</sub>, ACR or eGFR calculated using both formulas between the groups. There were weak negative correlations between U-Col4 and the NAG/creatinine<sub>u</sub> ratio ( $p = 0.02$ ,  $R = -0.27$ ) and between U-Col4 and ACR ( $p = 0.00$ ,  $R = -0.39$ ). Thus, there was also a moderate positive correlation between U-Col4/creatinine<sub>u</sub> ratio and the NAG/creatinine<sub>u</sub> ratio ( $p = 0.00$ ,  $R = 0.58$ ), and a weak positive correlation between the U-Col4/creatinine<sub>u</sub> ratio and ACR ( $p = 0.00$ ,  $R = 0.37$ ). No other correlations between the assessed parameters were found.

## Discussion

In the present study, we tried to answer whether U-Col4 is useful in assessing early renal impairment in CCSs. Our study is the first to evaluate U-Col4 in CCSs. The study group was homogeneous. None of the patients studied were diagnosed with CKD, hypertension, microalbuminuria or diabetes. Although for the purposes of the analysis we singled out patients after treatment, because nephroblastoma brings a potentially higher risk of nephrotoxicity, the parameters of renal function, including U-Col4, as well as the U-Col4/creatinine<sub>u</sub> ratio, were not significantly different between the groups. The main findings of our study are the correlations between U-Col4 and NAG/creatinine<sub>u</sub> ratio and between the U-Col4 and ACR.

Due to its relatively high molecular weight (540 kDa), U-Col4 is not filtered by the GBM [19]. Therefore, it is thought that its urinary excretion reflects the rate of matrix synthesis and degradation [20, 21]. There have been reports that low concentrations of U-Col4 can be found in the urine of healthy people [21]. Collagen excretion is thought to be little affected by factors such as fever, exercise, elevated blood pressure, lipid levels (versus



albumin) or muscle mass (versus creatinine) ([22, 23]). Age also seems irrelevant. The study by Nkuipou-Kenfack et al. found that among 116 peptides identified in the urine of a Japanese general population that showed a significant association with aging, type IV alpha-1 and alpha-3 basement membrane collagens accounted for only 2% [24].

In experimental studies on cultured mesangial cells, type IV collagen synthesis was induced by hypoxia and hyperglycemia [25]. In an animal model of CKD, proximal tubule cells were involved in collagen deposition in the peritubular space, confirming that collagen is involved in both glomerular and tubular damage [26]. This is why the correlation of U-Col4 and the NAG/creatinine<sub>u</sub> ratio that we have shown is particularly interesting. NAG is a glycosidase derived from proximal tubule epithelial cells. It is a specific marker of these cells. As with collagen, the relatively high molecular weight of NAG prevents its filtration by the GBM. An increase in NAG activity in urine may indicate damage to tubule cells [27].

U-Col4 appears to have several characteristics of a potential marker of kidney damage. The possibility of its non-invasive determination in a urine sample is an additional advantage particularly valuable in the pediatric population. Unfortunately, studies on U-Col4 have mainly concerned adults and diabetic nephropathy. U-Col4 concentration increases in the early stages of diabetic nephropathy, which is associated with both GBM thickening and fibrotic response in the course of the disease [22, 28]. According to the study by Cawood et al. [29], of three biomarkers of glomerular fibrosis [i.e. collagen IV,  $\alpha$ -glutathione-S-transferase (GST), and  $\pi$ GST] that they tested in diabetic patients, the most common abnormality was elevated levels of U-Col4 [29]. The percentage of patients with abnormal collagen levels increased gradually in groups from normo- through micro- to macroalbuminuria (26%, 58%, 65%, respectively) [29].

Other studies have found that increased U-Col4 levels in diabetic patients precede the onset of microalbuminuria. Furumatsu et al. [30] further proved that urinary protein concentration is an independent factor affecting U-Col4 in patients with nondiabetic kidney disease. They observed higher collagen concentrations in membranous nephropathies, with anti-neutrophil cytoplasmic antibodies (ANCA) and other diseases in which GBM is thickened [30].

No glycemc abnormalities and microalbuminuria were found in the patients we studied. Renal damage in patients after oncological treatment, as we mentioned, is the result of many factors. The different causes of kidney damage in these two clinical situations (i.e. diabetes and anti-neoplasm treatment) do not exclude the presence of similar morphological changes in the kidneys. According to the literature, glomerulopathy, as one of the components

of diabetic nephropathy, is associated with increased U-Col4 excretion. Among the case reports in CCSs, especially after nephrectomy, ours has found focal glomerulosclerosis leading to the development and progression of CKD [9]. Nevertheless, in the current study, patients after Wilms tumor treatment did not differ from the other groups in terms of renal function parameters, including U-Col4.

Most likely, the most important influence on the results of our study was the relatively short time elapsed since the end of anticancer treatment. As reported by Krawczuk-Rybak et al. [2], the risk of nephrotoxicity increases with the time elapsed since the end of treatment, and is highest after 15 years. In view of this, it would be valuable to extend our study through further prospective observations and assays. This idea is supported by a study by Kishi et al. [31] which showed that U-Col4 can be used as a predictor of worsening renal function in subjects without diabetes, overt proteinuria, or abnormal renal function. In their study, an abnormal U-Col4/creatinine<sub>u</sub> ratio was a significant and independent risk factor for a 10% change in eGFR over one year in patients with eGFR  $\geq 80$  mL/min/1.73 m<sup>2</sup> [31].

Our study has some limitations, which may have significantly impacted the results. These limitations include: the relatively small study population, the short time between the end of anti-neoplastic treatment and the time of the study, and the use of only single measurements of the parameters studied for analysis.

The question of the usefulness of U-Col4 in assessing early renal function damage in CCS remains open. The results obtained in patients with diabetic nephropathy and other kidney diseases are encouraging. Each year, the CCSs population is growing. This population requires regular FUP visits and tests to assess their renal function even many years after the end of treatment. The identification of new markers of renal function may help increase the sensitivity and specificity of our diagnostics. Finding substances that reflect the structural changes that occur with kidney damage would be particularly important as an alternative to invasive and complication-laden kidney biopsies.

U-Col4 has this potential, but the confirmation of this will require further well-designed clinical trials. The results of those trials should give us an opportunity to improve the health and quality of life of CCSs.

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### ***Authors' contributions***

MJ — gathering data, writing article. MJ, JS — data analysis and interpretation, research concept and design. JS — critical revision of article, supervision, final approval. AO — biochemical analysis.

### ***Conflict of interest***

The authors declare no conflict of interest.

### ***Financial support***

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### ***Informed consent statement***

Written informed consent was obtained from the legal guardians of the children and from those aged over 16.

### ***Data availability statement***

The analyzed data sets generated during this study are available from the corresponding author upon reasonable request for noncommercial use.

### ***Ethics***

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals, and approved by the Independent Bioethical Committee of Scientific Researchers at the Medical University of Gdansk (NKBBN/417/2014, 28<sup>th</sup> October 2014).

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