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Analysis of the dependence of the levels of markers of early kidney damage — cytokines KIM-1 and TGF-β1 in children with juvenile idiopathic arthritis

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Abstract. ***Background.*** *Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterized by chronic joint inflammation in children under the age of 16 years. Kidney damage in JIA ranges from asymptomatic proteinuria to severe glomerulonephritis that can lead to chronic kidney disease. Given the above data, the assumption of an increased risk of early development of kidney damage in children with JIA is reasonable. The purpose was to analyze the risk factors for structural tubular lesions by studying the level of kidney injury molecule-1 (KIM-1) and transforming growth factor β1 (TGF-β1) in children with JIA, depending on the characteristics of the clinical course of the disease and the treatment received.* ***Materials and methods.*** *Eighty children with JIA who were undergoing inpatient treatment at the Regional Medical Center for Family Health of the State Regional Health Department were examined. A retrospective analysis of medical documentation was conducted to assess the child's age at the onset of JIA, the duration of its course, clinical features, and treatment. Further, during the work, a clinical examination, assessment of the health of children, general clinical, biochemical, immunoenzymatic and immunological studies, ultrasound examination of joints and kidneys were performed. Structural tubular markers KIM-1 and TGF-β1 were measured in urine samples.* ***Results.*** *The average KIM-1 level was 0.9970 ± 0.1662 (0.98; 0.90–1.12) ng/ml, TGF-β1 — 20.26 ± 16.34 (14.02; 12.5–17.98) pg/ml. The average KIM-1 values varied depending on the form of JIA and the degree of disease activity. At the same time, with high JIA activity, the KIM-1 level was statistically significantly higher (1.1510 ± 0.0806 ng/ml, $p < 0.05$ compared to remission). A similar trend was observed when analyzing TGF-β1 levels. Elevated KIM-1 was associated with high JIA activity, involvement of ≥ 6 joints at the time of examination, and lesions of small joints of the hands and wrist joints. Elevated TGF-β1 was statistically significantly associated with polyarthritis, JIA duration of ≥ 6 years, and active disease stage of ≥ 4 years.* ***Conclusions.*** *Our study revealed a statistically significant relationship between the levels of KIM-1 and TGF-β1 biomarkers and the degree of JIA activity. The antinuclear antibodies status in patients with JIA did not affect the levels of KIM-1 and TGF-β1. Elevated content of KIM-1 and TGF-β1 in urine indicate the risk of structural kidney damage in patients with JIA. Risk factors are high JIA activity, significant joint involvement, prolonged active stage, the presence of hypertension, and NSAIDs treatment. The combination of NSAIDs with methotrexate increased the levels of KIM-1 and TGF-β1, which indicated a nephrotoxic effect, while the combination of methotrexate with immunobiological drugs decreased the levels of biomarkers.*

Keywords: *juvenile idiopathic arthritis; kidneys; children; markers of early kidney damage; KIM-1; TGF-β1*

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterized by chronic joint inflammation in children under 16 years of age [1]. Although the main lesion affects the musculoskeletal system, systemic inflammation and the therapy administered can negatively affect renal function, increasing the risk of developing nephropathies [2, 3]. Renal damage in JIA ranges from asymptomatic proteinuria to severe glomerulonephritis, which can lead to chronic kidney disease (CKD) [3]. The main mechanisms

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of renal damage in JIA are as follows. On the one hand, inflammatory activity associated with the hyperproduction of proinflammatory cytokines, which causes systemic inflammation, leads to endothelial dysfunction and impaired renal microcirculation. On the other hand, drug-induced nephrotoxicity due to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and methotrexate (MTX) can cause acute kidney injury and interstitial nephritis. Concomitant autoimmune disorders accompanied by signs of immune complex glomerulonephritis are also considered to be causally significant [3–5].

Only one retrospective cohort study has evaluated the prevalence of CKD in children with JIA. It was found that 8 % of children had hypertension or minimal proteinuria 65 months after onset [6].

Given the above data, the assumption of an increased risk of early development of kidney damage in children with JIA is reasonable. At the same time, the need for timely correction of CKD emphasizes the importance of non-invasive methods of diagnosing this condition using renal biomarkers [7]. Among these biomarkers, the most important are kidney injury molecule-1 (KIM-1) and transforming growth factor β1 (TGF-β1) [8, 9].

KIM-1 is a transmembrane glycoprotein expressed by proximal tubular cells and is recognized as an early, sensitive, and specific urinary biomarker of kidney damage [10]. KIM-1 has anti-inflammatory and protective properties, as it can convert epithelial cells into semi-professional phagocytes by binding phosphatidylserine to dead cells [11]. However, chronic overexpression of KIM-1 in tubular cells can lead to inflammation and interstitial fibrosis [12]. Renal fibrosis, regardless of its etiology, is the final common stage of almost all chronic kidney diseases [13, 14].

In the context of fibrosis, the most widely studied renal marker that plays an important role in the progression of CKD is TGF-β1 [15]. Uncontrolled or excessive activation of the TGF-β signaling pathway in the absence of regulatory mechanisms can lead to pathological consequences, in particular, to persistent epithelial-mesenchymal transdifferentiation, which contributes to impaired cellular differentiation, induction of apoptosis and excessive synthesis of extracellular matrix [16]. Its significance as a therapeutic target is due to its role in the pathogenesis of renal fibrosis in CKD [17].

There are no studies in the available literature regarding the levels of real biomarkers KIM-1 and TGF-β1 in children with JIA. Determination of them in urine is important, as it allows for timely detection of tubular structural damage to the kidneys, as well as identifying risk factors for early development of renal fibrosis.

The purpose of the study was to analyze the risk factors for the development of structural tubular lesions by evaluating the level of KIM-1 and TGF-β1 in children with JIA, depending on the characteristics of the clinical course of the disease and the treatment received.

Materials and methods

An open-cohort prospective study of children with JIA who were inpatients at the Regional Medical Center for Family Health of the State Regional Health Department was conducted. It was performed in accordance with the principles of the Declaration of Helsinki. The Local Ethics Committee approved the study protocol.

Inclusion criteria: a diagnosis of JIA according to EULAR criteria [18], and informed parental consent to participate in the study. Exclusion criteria: congenital malformations of the urinary system, history of acquired urinary diseases or their presence at the time of the study.

A retrospective analysis of medical records was conducted to assess the child's age at the onset of the disease, duration of the course, clinical features of JIA, and treatment. At the time of the study, a clinical examination was performed, the health status of children was assessed according to the Childhood Health Assessment Questionnaire [19], general clinical (blood and urine analysis), biochemical (serum creatinine and eGFR according to the Schwartz formula [20], blood urea, C-reactive protein), immunoenzymatic (antinuclear antibodies, HLA B27 antigen) and immunological (rheumatoid factor) methods, ultrasound of joints and kidneys.

To measure the structural tubular markers KIM-1 and TGF-β1 in urine samples, we used a solid-phase enzyme-linked immunosorbent assay according to the manufacturer's instructions [21, 22].

A set of statistical research methods was applied, namely: for independent samples — Mann-Whitney test, for dynamics assessment — McNemar's test, for correlation tables — χ^2 test and Fisher's exact test, for assessing the degree of dependence between variables — Spearman correlation. Data analysis was performed using the Statistica 6.1® software product (StatSoft Inc., serial number AGAR909E415822FA).

Results and discussion

We examined 80 children with JIA aged 10.40 ± 4.41 (10.6–15.0) years. Girls slightly predominated by gender — 46 (57.5 %). The onset of JIA was recorded at the age of 5.80 ± 4.14 (4.9; 2.9) years. The clinical course of JIA had the following variants: systemic arthritis — 9 (11.3 %), polyarthritis — 47 (58.8 %), oligoarthritis — 24 (30.0 %). The activity of the disease was determined by the Juvenile Arthritis Disease Activity Score [23]. JIA remission was diagnosed in 60 children, low activity — in 14, high activity — in 6.

At the time of examination, all patients were receiving MTX, 22 children (27.5 %) took NSAIDs, and 25 (31.3 %) were receiving immunobiological drugs (IBDs).

During standard nephrological examination of patients (general urine analysis, serum creatinine and urea values, renal ultrasound), no pathological changes were detected. The eGFR indicator based on serum creatinine analysis according to the Schwartz formula for three months corresponded to the normative values.

On average, KIM-1 was 0.9970 ± 0.1662 (0.98; 0.90–1.12) ng/ml, TGF-β1 was 20.26 ± 16.34 (14.02; 12.5–17.98) pg/ml. The study evaluated the levels of KIM-1 and TGF-β1 in the urine of children with different forms of JIA, taking into account the stage of disease activity and the presence of antinuclear antibodies (ANA) (Table 1).

The average KIM-1 values varied depending on the form of JIA and the degree of disease activity. In patients with per-

sistent oligoarthritis and systemic arthritis, they were almost the same: 0.9620 ± 0.1445 ng/ml and 0.9610 ± 0.2072 ng/ml, respectively. In children with polyarthritis, this indicator was slightly higher — 1.0210 ± 0.1674 ng/ml but did not have a statistically significant difference.

In remission of JIA, the average level of KIM-1 was 0.9850 ± 0.1730 ng/ml, in patients with low JIA activity — 0.9820 ± 0.1323 ng/ml, in the JIA group with ANA+ status — 0.9940 ± 0.1921 ng/ml. At the same time, with high JIA activity, the level of KIM-1 was significantly higher (1.1510 ± 0.0806 ng/ml, $p < 0.05$ compared to remission), which indicated a high probability of kidney damage in these patients.

A similar trend was observed in the analysis of TGF-β1 levels. In patients with persistent oligoarthritis, the mean TGF-β1 was 15.010 ± 5.380 pg/ml, and in the polyarthritis, it was slightly higher (23.020 ± 18.773 pg/ml), while in systemic arthritis, the values were intermediate (19.880 ± 19.985 pg/ml), $p > 0.05$.

In patients in remission, the level of TGF-β1 was 18.920 ± 15.041 pg/ml, while with low activity, it increased slightly (22.220 ± 9.851 pg/ml). The highest levels of TGF-β1 were observed in patients with high JIA activity (29.150 ± 34.198 pg/ml, $p < 0.05$ compared to remission), which may indicate an increase in fibrotic processes in the renal tissue during exacerbation of the inflammatory process. The results obtained are consistent with the findings of P.C. Tang et al. who noted that short-term activation of TGF-β1 promotes renal tissue recovery, while its prolonged activation leads to fibrosis and progression of CKD [24].

Analysis of KIM-1 and TGF-β1 levels depending on ANA status did not reveal significant differences between ANA+ (0.9940 ± 0.1921 ng/ml, 19.500 ± 18.580 pg/ml) and ANA– patients (0.9980 ± 0.1577 ng/ml, 20.530 ± 15.632 pg/ml). This indicated that the presence of antinuclear antibodies did not significantly affect the content of these biomarkers.

We also assessed biomarker levels depending on the characteristics of JIA therapy, in particular the use of MTX, NSAIDs, and IBDs (Table 2).

In patients receiving only MTX without additional NSAIDs, the mean KIM-1 level was 0.9790 ± 0.1731 ng/ml, with a trend but no statistically significant difference with the group of children taking combined MTX + NSAIDs therapy (1.0420 ± 0.1397 ng/ml).

Analysis of the TGF-β1 marker revealed that in patients receiving MTX alone, the mean level was 18.100 ± 14.105 pg/ml, while in the group of patients taking NSAIDs as well, it was statistically significantly higher (25.970 ± 20.430 pg/ml, $p < 0.001$). This indicated a possible effect of NSAIDs on an increase in the level of markers of renal damage.

Concerning IBDs, in patients receiving MTX alone, the mean KIM-1 level was 1.0360 ± 0.1337 ng/ml, while in the group with additional use of immunobiological drugs, it was significantly lower (0.9100 ± 0.1979 ng/ml, $p < 0.01$).

The level of TGF-β1 also showed a significant decrease in children treated with immunobiological therapy:

Table 1. Cytokine indices in the urine of patients depending on the forms and markers of JIA activity, M ± s (Me; Q_1-Q_3)

Indicator	KIM-1, ng/ml	TGF-β1, pg/ml
Persistent oligoarthritis, n = 24	0.9620 ± 0.1445 (0.94; 0.85–1.04)	15.010 ± 5.380 (13.52; 12.22–14.79)
Polyarthritis, n = 47	1.0210 ± 0.1674 (1.03; 0.92–1.17)	23.020 ± 18.773 (15.08; 12.72–24.48)
Systemic arthritis, n = 9	0.9610 ± 0.2072 (0.98; 0.83–1.12)	19.880 ± 19.985 (13.37; 11.6–15.85)
Remission, n = 60	0.9850 ± 0.1730 (0.97; 0.87–1.11)	18.920 ± 15.041 (13.44; 12.18–15.31)
Low activity, n = 14	0.9820 ± 0.1323 (0.98; 0.92–1.09)	22.220 ± 9.851 (18.38; 15.68–27.88)**
High activity, n = 6	1.1510 ± 0.0806 (1.17; 1.08–1.22)*^	29.150 ± 34.198 (15.21; 14.02–37.95)*
ANA–, n = 59	0.9980 ± 0.1577 (0.98; 0.91–1.11)	20.530 ± 15.632 (13.54; 12.19–20.6)
ANA+, n = 21	0.9940 ± 0.1921 (0.98; 0.85–1.17)	19.500 ± 18.580 (14.38; 13.51–16.98)

Notes: *, ** — significant difference from the sample with remission; ^ — from the sample with high JIA activity ($p < 0.05$); no significant effect of JIA forms or the presence of ANA on the cytokine profile was found in any case (Mann-Whitney test was used).

Table 2. Indicators of biomarkers in the urine of patients depending on the characteristics of JIA therapy, M ± s (Me; Q_1-Q_3)

Biomarkers	MTX + NSAIDs		MTX + IBDs	
	No, n = 58	Yes, n = 22	No, n = 55	Yes, n = 25
KIM-1, ng/ml	0.9790 ± 0.1731 (0.97; 0.87–1.11)	1.0420 ± 0.1397 (1.06; 0.93–1.16)	1.0360 ± 0.1337 (1.01; 0.93–1.15)	0.9100 ± 0.1979 (0.91; 0.76–1.05)*
TGF-β1, pg/ml	18.100 ± 14.105 (13.4; 12.18–15.01)	25.970 ± 20.430 (17.69; 14.84–27.88)**	22.760 ± 18.823 (14.4; 13.32–22.15)	14.760 ± 5.994 (12.92; 12.04–14.05)*

Notes: *, ** — significant difference from reference levels: $p < 0.01$ and $p < 0.001$, respectively (Mann-Whitney test was used).

Table 3. Factors associated with increased urinary biomarkers

Factor	KIM-1		TGF-β1	
	OR (95% CI)	p	OR (95% CI)	p
OR > 1 (increased odds of structural damage)				
Polyarthritis	NS		3.74 (1.12–12.51)	0.04
JIA activity is high	7.25 (1.22–43.22)	0.04	NS	
Affection of ≥ 6 joints during the examination period	5.00 (1.65–15.15)	0.006	NS	
Arthritis of the small joints of the hand	4.85 (1.39–16.87)	0.02	NS	
Arthritis of the wrist joints	3.78 (1.21–11.83)	0.03	NS	
Hip arthritis	10.41 (1.02–106.7)	0.05	NS	
JIA duration ≥ 6 years	NS		2.96 (1.01–8.66)	0.05
Active stage ≥ 4 years	NS		6.11 (2.01–18.58)	0.002
Caries	NS		3.24 (1.14–9.22)	0.04
Hypertension	12.43 (2.26–68.27)	0.003	6.33 (1.36–29.55)	0.03
Erythrocyte sedimentation rate above normal	NS		4.33 (1.35–13.88)	0.02
Use of NSAIDS	NS		4.00 (1.36–11.79)	0.02
OR < 1 (reduced odds of structural damage)				
Male gender	NS		0.17 (0.04–0.62)	0.005
Immunobiological therapy	NS		0.18 (0.04–0.84)	0.03

Notes: OR — odds ratio; CI — confidence interval; NS — not significant.

in patients receiving MTX alone, the level of TGF-β1 was 22.760 ± 18.823 pg/ml, while in the group with combined MTX + IBDs therapy, this indicator was statistically significantly lower (14.760 ± 5.994 pg/ml, $p < 0.01$).

In our study, we analyzed factors that have a statistically significant association with increased levels of biomarkers of renal injury, KIM-1 and TGF-β1, in the urine of children with JIA (Table 3).

Elevated KIM-1 levels were associated with high JIA activity (OR = 7.25; 95% CI: 1.22–43.22; $p = 0.04$), involvement of ≥ 6 joints at the time of examination (OR = 5.00; 95% CI: 1.65–15.15; $p = 0.006$), as well as involvement of small joints of the hands (OR = 4.85; 95% CI: 1.39–16.87; $p = 0.02$) and wrist joints (OR = 3.78; 95% CI: 1.21–11.83; $p = 0.03$).

A significant risk factor was hip arthritis, which was associated with the highest odds of increased KIM-1 (OR = 10.41; 95% CI: 1.02–106.7; $p = 0.05$). In addition, a relationship was found with the presence of hypertension, which had a pronounced effect on the level of KIM-1 (OR = 12.43; 95% CI: 2.26–68.27; $p = 0.003$). According to the studies of J. Song et al., the level of KIM-1 in urine is a biomarker of CKD associated with arterial hypertension [25].

Experimental data conducted by C. Yin and N. Wang, confirm our data on the role of KIM-1 in the development of CKD, namely: a persistent increase in the level of KIM-1 contributes to the occurrence and development of renal fibrosis [26].

Elevated TGF-β1 levels were statistically significantly associated with polyarthritis (OR = 3.74; 95% CI: 1.12–12.51; $p = 0.04$), duration of JIA ≥ 6 years (OR = 2.96; 95% CI: 1.01–8.66; $p = 0.05$), and active disease stage ≥ 4 years (OR = 6.11; 95% CI: 2.01–18.58; $p = 0.002$).

TGF-β1 levels were also elevated in patients with hypertension (OR = 6.33; 95% CI: 1.36–29.55; $p = 0.03$), caries (OR = 3.24; 95% CI: 1.14–9.22; $p = 0.04$), and increased erythrocyte sedimentation rate (OR = 4.33; 95% CI: 1.35–13.88; $p = 0.02$). NSAIDs use was associated with a significant increase in TGF-β1 levels (OR = 4.00; 95% CI: 1.36–11.79; $p = 0.02$). Our results are consistent with those of M.F. Gicchino et al. who found that the main risk factor for the development of kidney damage in children with JIA was long-term exposure to NSAIDs and methotrexate during active forms of the disease [6].

Two factors were protective against TGF-β1 rise. Male gender reduced the risk of elevated TGF-β1 levels by more than fivefold (OR = 0.17; 95% CI: 0.04–0.62; $p = 0.005$). In addition, IBDs use, reducing TGF-β1 elevation by almost sixfold (OR = 0.18; 95% CI: 0.04–0.84; $p = 0.03$), exerted a significant nephroprotective effect.

Conclusions

Our study revealed a statistically significant relationship between the levels of KIM-1 and TGF-β1 biomarkers and the degree of JIA activity. The ANA status in JIA patients did not affect the levels of KIM-1 and TGF-β1 biomarkers.

Elevated urinary KIM-1 and TGF-β1 indicate a risk of structural kidney damage in patients with JIA. Risk factors include high JIA activity, significant joint involvement, prolonged active phase, presence of hypertension, and NSAIDs treatment.

The combination of NSAIDs and MTX increased the levels of KIM-1 and TGF-β1, indicating a nephrotoxic effect, while the combination of MTX with IBDS decreased the levels of biomarkers.

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Аналіз залежності рівнів маркерів раннього ураження нирок — цитокінів КІМ-1 та TGF-β1 у дітей, хворих на ювенільний ідіопатичний артрит

Резюме. Актуальність. Ювенільний ідіопатичний артрит (ЮІА) є гетерогенною групою захворювань, що характеризуються хронічним запаленням суглобів у дітей віком до 16 років. Ураження нирок при ЮІА варіюють від безсимптомної протеїнурії до тяжкого гломерулонефриту, здатного призвести до хронічної хвороби нирок. З огляду на наведені дані припущення про підвищений ризик раннього ураження нирок у дітей із ЮІА є обґрунтованим. **Мета роботи:** проаналізувати фактори ризику розвитку структурних тубулярних уражень шляхом вивчення рівня молекули ушкодження нирок-1 (KIM-1) і трансформуючого фактора росту β1 (TGF-β1) у дітей із ЮІА залежно від особливостей клінічного перебігу захворювання та отриманого лікування. **Матеріали та методи.** Обстежено 80 дітей із ЮІА, які знаходились на стаціонарному лікуванні в КП «Регіональний медичний центр родинного здоров'я» ДОР. Проведений ретроспективний аналіз медичної документації з оцінкою віку дитини в дебюті захворювання на ЮІА, тривалості його перебігу, клінічних особливостей і лікування. У подальшому під час виконання роботи проводили клінічне обстеження, оцінку стану здоров'я дітей, загальноклінічні, біохімічні, імуноферментні й імунологічні дослідження, ультразвукове дослідження суглобів та нирок. Для визначення структурних тубулярних маркерів KIM-1 і TGF-β1 у зразках сечі використовували імуноферментний аналіз. **Результати.** У середньому показник KIM-1 дорівнював 0,9970 ± 0,1662 (0,98; 0,90–1,12) нг/мл, TGF-β1 — 20,26 ± 16,34 (14,02; 12,5–17,98) пг/мл. Середні значення KIM-1 варіювали залежно від форми ЮІА та ступеня активності захворювання. Водночас при високій активності ЮІА рівень KIM-1 був статистично значуще вищим (1,1510 ± 0,0806 нг/мл, $p < 0,05$ порівняно з ремісією). Подібна тенденція спостерігалася і при аналізі TGF-β1. Підвищений уміст KIM-1 асоціювався з високою активністю ЮІА, залученням ≥ 6 суглобів на момент обстеження, а також ураженням дрібних суглобів кистей рук та променевозап'ясткових суглобів. Підвищений рівень TGF-β1 був статистично значуще асоційований із поліартритом, тривалістю ЮІА ≥ 6 років та активною стадією захворювання ≥ 4 років. **Висновки.** У нашому дослідженні виявлена статистично значуща залежність умісту біомаркерів KIM-1 та TGF-β1 від ступеня активності ЮІА. Статус антинуклеарних антитіл у пацієнтів з ЮІА не впливав на динаміку KIM-1 і TGF-β1. Підвищені рівні KIM-1 і TGF-β1 у сечі вказують на ризик структурного ураження нирок у пацієнтів з ЮІА. Факторами ризику є висока активність ЮІА, значне залучення суглобів, тривала активна стадія, наявність артеріальної гіпертензії, лікування НПЗП. Комбінація НПЗП та метотрексату підвищувала рівні KIM-1 і TGF-β1, що свідчило про нефротоксичну дію, тоді як комбінація метотрексату з імунобіологічними препаратами знижувала вміст біомаркерів.

Ключові слова: ювенільний ідіопатичний артрит; нирки; діти; маркери раннього ураження нирок; KIM-1; TGF-β1