CLINICAL NEPHROLOGY
ORIGINAL SCIENTIFIC PAPERS

Adv Clin Exp Med 2008, **17**, 2, 129–135
ISSN 1230-025X

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Assessment of Urinary Collagen Type IV Excretion in Children with IgA Nephropathy

Ocena wydalania kolagenu IV w moczu dzieci z nefropatią IgA

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Abstract

Background. IgA nephropathy (IgAN) may lead to end-stage renal failure due to renal fibrosis with accumulation of extracellular matrix proteins such as collagen IV (Col IV).
Objectives. The aim of the study was to evaluate urinary Col IV excretion in children with IgAN as a marker of chronic glomerulonephritis activity.
Material and Methods. Twenty-four-hour urinary Col IV excretion (in ng/mg creatinine) was measured in 20 children with IgAN (mean age: 13.52 ± 3.5 years) at a mean time of 4.33 ± 2.4 years from the onset of illness and in 18 healthy children (mean age: 10.5 ± 4.2, control group K). IgAN was diagnosed based on renal biopsy. The severity of histological changes in the renal biopsy was determined by light microscopy based on the WHO classification in grades I–V. Children with IgAN were divided in two groups: group A with proteinuria at the onset of illness and group B without proteinuria. To evaluate baseline Col IV based on the severity of renal lesions as assessed in the renal biopsy using the WHO classification, the patients were divided in two groups: group I included children with grade I–II and group II children with grade III–IV renal lesions.
Results. Mean collagen IV urine excretion in group A (62.68 ± 90.55 ng/mg creatinine) was higher than in group B (27.96 ± 19.69; ns.) and significantly higher than in group K (12.13 ± 4.6, $p < 0.01$). Children with WHO grade III–IV renal lesions (group II) had insignificantly higher mean urinary Col IV levels than children with WHO grade I–II renal lesions (group I). Mean urinary Col IV levels in groups I and II were significantly higher than in the control group (group I vs. K: $p < 0.01$, group II vs. K: $p < 0.05$). Positive correlation between urinary Col IV level at baseline and the severity of proteinuria at the onset of illness was found ($r = 0.71$, $p < 0.05$).
Conclusions. The dynamic changes in urinary Col IV level seen in children with IgAN and its positive correlation with the presence of proteinuria in the course of the disease suggest that determination of urinary Col IV excretion may be a useful marker of the activity of nephropathy (**Adv Clin Exp Med 2008, 17, 2, 129–135**).

Key words: IgA nephropathy, collagen IV, children.

Streszczenie

Wprowadzenie. Nefropatia IgA (IgAN) może prowadzić do przewlekłej niewydolności nerek wskutek włóknienia tkanki nerkowej, w czym bierze udział kolagen IV (*col IV*).
Cel pracy. Ocena wydalania kolagenu IV w moczu u dzieci z nefropatią IgA jako wskaźnika aktywności przewlekłego procesu zapalnego w nerkach.
Materiał i metody. Badaniami objęto 20 dzieci z IgAN średnio w wieku 13,52 ± 3,5 roku, oraz 18 zdrowych dzieci średnio w wieku 10,5 ± 4,2 (grupa K), u których oznaczono stężenie *col IV* w dobowej zbiórce moczu (w ng/mg kreatyniny) w średnim czasie 4,33 ± 2,4 roku od początku choroby, przez okres 24 miesięcy. IgAN w grupie badanej rozpoznano na podstawie biopsji nerki. Zmiany histopatologiczne sklasyfikowano w stopniach I–V wg WHO. Pacjentów z IgAN podzielono na 2 grupy: A – z białkomoczem na początku choroby, B – bez białkomoczu. Wydalanie *col IV* analizowano także w zależności od stopnia zmian w nerkach wg klasyfikacji WHO w grupach: I–I/II stopień, II–III/IV stopień.
Wyniki. Średnie stężenie *col IV* w moczu dzieci z grupy A (62,68 ± 90,55 ng/mg kreatyniny) było większe niż grupy B (27,96 ± 19,69; ns.) istotnie większe niż w grupie K (12,13 ± 4,6; $p < 0,01$). U dzieci z III/IV stopniem zaawansowania zmian w biopsji nerki wg klasyfikacji WHO (grupa II) stwierdzono większe, ale nieistotnie, średnie wartości stężenia kolagenu IV niż w grupie z I/II stopniem wg klasyfikacji WHO (grupa I). Średnie stężenie kolagenu IV w moczu u dzieci z grupy I i II było istotnie większe niż w grupie kontrolnej (grupa I *vs* K $p < 0,01$; gru-

pa II *vs* K $p < 0,05$). Stwierdzono dodatnią korelację ($r = 0,071$, $p < 0,05$) między stężeniem *col IV* w moczu dzieci z IgAN na początku obserwacji, a białkomoczem na początku choroby.
Wnioski. Stwierdzenie dynamiki zmian stężenia *col IV* w moczu oraz dodatniej korelacji z białkomoczem u dzieci z IgAN w przebiegu choroby może być dowodem przydatności oznaczania tego markera jako wskaźnika aktywności nefropatii (**Adv Clin Exp Med 2008, 17, 2, 129–135**).

Słowa kluczowe: nefropatia IgA, kolagen IV, dzieci.

IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide that may result in chronic renal failure (CRF). Progression of nephropathy in patients with IgAN is seen already in childhood, with CRF developing in 5–30% of patients at 10 years and 25–50% of patients at 20 years. Complete disease remission has been reported in 3–30% of patients [1–6].

Due to the varying presenting symptoms and inconsistent data from long-term follow-up, the individual risk of progression of nephropathy and the development of CRF is difficult to establish. Current research efforts focus on identifying factors affecting the progression of IgAN as such factors might have prognostic value and thus would be helpful in defining more uniformly accepted indications for treatment, which have not yet been clearly standardized.

Many authors believe that renal dysfunction depends mainly on interstitial and tubular fibrosis which might result from an accumulation of extracellular matrix proteins such as fibronectin, collagen type IV (Col IV), and laminin. A hypothesis has been put forward suggesting that the accumulation of extracellular matrix proteins is related to the activation of interstitial fibroblasts, migration of mesenchymal stem cells from the bone marrow, or transformation of renal tubular epithelium into cells producing extracellular matrix proteins. Other authors indicate the critical role played by interstitial fibroblast-derived myofibroblasts in tubulointerstitial fibrosis, as proliferation of these cells and their association with the production of transforming growth factor-β and Col IV have been reported both in experimental models and clinical studies [7–9]. Deposits of Col IV are seen among damaged renal tubular cells and transformed interstitial cells. Interstitial myofibroblasts and epithelial cells in the damaged renal tubules are responsible for interstitial fibrosis [10–12].

One research avenue pursued by many interested in this area has been a search for markers of the activity of chronic glomerulonephritis by assessing the severity of fibrosis based on determination of fibronectin, Col IV, and laminin levels in various body fluids. The objective of this study was to assess urinary Col IV excretion in children with IgAN as a marker of the activity of chronic inflammatory process in the kidney.

Material and Methods

Twenty children with IgAN aged 3–17.7 years who were hospitalized at the Department of Pediatric Nephrology, Medical University of Warsaw, in 1994–2004 were studied. In all patients the course of the disease was retrospectively and/or prospectively analyzed with particular attention to clinical signs and symptoms, abnormal laboratory findings including 24-hour urinary Col IV excretion, and histological evaluation of renal biopsy specimens. The following laboratory tests were performed in the studied group of 20 children at baseline, then every 6 months during the first year of follow-up, and at 24 months:

a) blood tests: urea, creatinine, cholesterol, triglycerides, total protein, albumin, immunoglobulins, and complement proteins C3 and C4;

b) urine tests: protein and erythrocyturia in spot urine samples; protein, creatinine, and Col IV in 24-hour urine collection.

The control group consisted of 18 healthy children. Laboratory evaluation in this group included 24-hour urinary Col IV excretion, urinalysis, and measurements of serum urea and creatinine levels.

Col IV excretion in 24-hour urine collection was determined by an immunoenzymatic competitive method using Sigma kits and expressed as ng/mg creatinine. These determinations were performed in a specialized Laboratory at the Department of Immunology, Transplantology, and Internal Medicine, Medical University of Warsaw and the results obtained in the study group were compared with those of the control group.

The diagnosis of IgAN in all patients was made based on the results of renal biopsy. The severity of histological changes in the renal biopsy was determined using light microscopy based on the World Health Organization (WHO) classification [6]. Grade I lesions are defined as minimal changes. Grade II lesions show mesangial proliferation involving less than 50% of glomeruli, with single small crescents and no interstitial and tubular changes. Grade III lesions are defined as diffused mesangial proliferation with focal and segmental variations; adhesions and small crescents are occasionally present; this histological picture is defined as focal and segmental glomerulonephritis; focal interstitial edema and mild infil-

trates are occasionally present. Grade IV lesions are when all the glomeruli show marked diffuse mesangial proliferation and sclerosis with varying degrees of hypercellularity and irregular distribution of lesions; up to 50% of glomeruli contain adhesions and crescents; these lesion characterize diffuse mesangial proliferative glomerulonephritis; tubular and interstitial inflammation are evident. Grade V lesions are defined as segmental and/or global glomerular sclerosis, hyalinosis and capsular adhesions; crescents in more than 50% of glomeruli, infiltrates in the interstitial tissue, and tubular atrophy more severe than in grade IV.

Immunofluorescence (IF) testing was performed using indirect IF assay with monoclonal IF sera (DAKO).

The results are expressed as the mean and median values and standard deviations. The Shapiro-Wilks, Student's *t*, and the Bartlett tests were used in the statistical analyses, with the level of statistical significance set at $p < 0.05$. All statistical analyses were performed using the STATGRAPHICS 4 Plus software.

Results

The mean age at the onset of IgAN was 10.09 ± 3.64 years (range: 3–17.7 years). The age at the onset of the disease in boys (11.09 ± 3.06 years) was significantly higher compared with that of the girls (7.08 ± 3.91 years, $p < 0.05$). IgAN was diagnosed based on renal biopsy and significantly more commonly ($p < 0.05$) found in boys (75% patients).

The most common presenting signs of nephropathy in the 20 studied children included macro- or microscopic erythrocyturia in all patients and proteinuria in 12 (60%) patients, including proteinuria in the nephrotic range in 5 (42%) patients and non-nephrotic-range proteinuria in 7 (58%) patients. One patient presented with full-blown nephrotic syndrome.

Macroscopic erythrocyturia was found in 8 (40%) patients. Isolated microscopic erythrocyturia was found in 6 (30%) patients, and the remaining 6 patients also presented with proteinuria, including nephrotic-range proteinuria in 3 patients. Among the 8 children with macroscopic erythrocyturia, 6 (75%) also had proteinuria, including 2 patients (33%) with nephrotic-range proteinuria and 4 (67%) patients with non-nephrotic-range proteinuria. The remaining 2 (25%) patients presented with isolated macroscopic erythrocyturia.

In 3 children (15%), high blood pressure was seen in the initial phase of the disease.

Laboratory Tests

The laboratory test results at baseline were compared in two groups of patients. Group A included 12 children with proteinuria and group B 8 children without proteinuria (Table 1). No significant differences were found between groups A and B with regard to mean age, erythrocyturia, mean IgA, IgG, and IgM levels, serum complement proteins C3 and C4, urea and creatinine levels, and glomerular filtration rate. Mean total protein and albumin levels were insignificantly lower in group A than in group B. Lipid levels were insignificantly higher in group A than in group B.

Renal Biopsy

Renal biopsy was performed in all patients at the onset of the disease. The mean time from the initial symptoms of the disease to the biopsy was 1.06 ±1.37 years. The mean age of the children at the time of the biopsy was 11.14 ± 3.48 years (group A: 10.5 ± 3.97 years, group B: 12.08 ± 2.53 years, p = NS). WHO classification grade I histological changes in the renal biopsy were found in 2 (10%) children, grade II changes in 9 (45%) children, grade III changes in 8 (40%) children, and grade IV changes in one (5%) child.

Collagen type IV Determination

The mean age of the children at the time of Col IV level determination was 13.52 ± 3.5 years. The mean time since the onset of disease to the initial determination of urinary Col IV excretion in the children with IgAN was 4.33 ± 2.4 years (range: 0.4–10 years). The present analysis includes data on urine testing in 17 patients. Urinary Col IV levels in patients with IgAN were analyzed at baseline (Col IV 0) and at 24 months of follow-up (Col IV 24) in relation to the presence of proteinuria at baseline and the severity of renal lesions as assessed in the renal biopsy using the WHO classification as the risk factors for disease progression. The patients were divided into two groups: group A (with proteinuria, n = 11) and group B (without proteinuria, n = 6) at the onset of illness.

Mean Col IV 0 values in the groups A and B and the control group are shown in Figure 1. The mean urinary Col IV 0 level was insignificantly higher in group A than in group B, and in both groups of patients with IgAN it was significantly higher than in the control group (group A vs. controls: $p < 0.05$, group B vs. controls: $p < 0.01$).

Table 1. Mean values of biochemical parameters in children with IgA nephropathy in groups A and B

Tabela 1. Średnie wartości parametrów biochemicznych na początku choroby u dzieci z nefropatią IgA w grupach A i B

	Parameter (Parametr badany)	Group A (Grupa A) (n = 12)	Group B (Grupa B) (n = 8)	p
	Age at the onset – years (Wiek zachorowania – lata)	9.32 ± 4.12	11.24 ± 2.62	ns.
Urine tests (Badanie moczu)	proteinuria (białkomocz) mg/kg/d	46.35 ± 44.94	0	–
	proteinuria (białkomocz) g/d	1.48 ± 1.16	0	–
	hematuria (krwinkomocz)	147.5 ± 109.0	125.0 ±107.3	ns.
Immunoglobulins (Immunoglobuliny)	IgA mg/dl	262.7 ± 165.5	304.1 ± 189.2	ns.
	IgG mg/dl	957.5 ± 353.2	1320.8 ± 527.2	p = 0.08 B > A
	IgM mg/dl	157.3 ± 93.8	156.7 ± 70.0	ns.
Complement (Składowe dopełniacza)	C3 mg/dl	123.1 ± 36.6	124.6 ± 26.8	ns.
	C4 mg/dl	23.0 ± 7.3	23.3 ± 8.4	ns.
Renal function (Wykładniki funkcji nerek)	urea (mocznik) mg/dl	31.23 ± 11.31	27.78 ± 11.12	ns.
	creatinine (kreatynina) mg/dl	0.59 ± 0.15	0.58 ± 0.11	ns.
	GFR ml/min	148.8 ± 51.96	151 ± 37.76	ns.
Proteins (Białka)	total proteins (białko całkowite) g%	6.46 ± 1.18	7.28 ± 0.81	ns.
	albuminy g%	3.69 ± 0.75	3.99 ± 0.55	ns.
Lipids (Lipidy)	cholesterol mg/dl	214.5 ± 72.4	189.63 ± 33.17	ns.
	TG mg/dl	120.42 ± 45.73	72.35 ± 83.3	ns.

To evaluate Col IV 0 based on the severity of renal lesions as assessed in the renal biopsy using the WHO classification, the patients were divided in two groups: group I (n = 9) included children with WHO grade I–II renal lesions and group II (n = 8) children with WHO grade III–IV renal lesions. Mean Col IV 0 values in groups I and II are shown in Figure 2. Children with WHO grade III–IV renal lesions (group II) had insignificantly higher mean urinary Col IV level than children with WHO grade I–II renal lesions (group I). The mean urinary Col IV level in groups I and II was significantly higher than in the control group (group I vs. controls: $p < 0.01$, group II vs. controls: $p < 0.05$).

The relationship between urinary Col IV level at baseline and the severity of proteinuria at the onset of illness was also analyzed in children with IgAN. The results of this analysis are shown in Figure 3. In all patients with IgAN there was a positive correlation between urinary Col IV level at baseline and the severity of proteinuria at baseline ($r = 0.37$, $p < 0.05$). In 11 children with IgAN and proteinuria at baseline (Group A), a positive correlation was also found between urinary Col IV level at baseline and the severity of proteinuria at the onset of illness ($r = 0.71$, $p < 0.05$). Among patients with IgAN there was no correlation between urinary Col IV level at baseline and the severity of renal lesions using the WHO classification in the renal biopsy specimens.

Urinary Col IV levels at 24 months (Col IV 24) were also analyzed in relation to clinical signs and

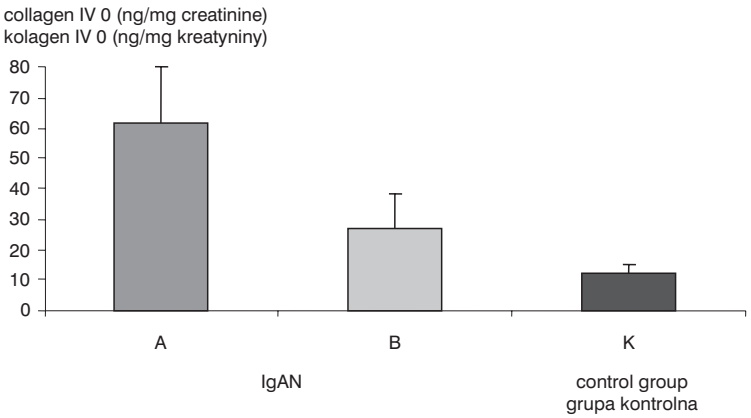

Fig. 1. Mean values of urine collagen IV in children with IgA nephropathy in groups A, B, and the control group (K) at the onset of observation

Ryc. 1. Średnie wartości stężenia kolagenu IV w moczu na początku obserwacji u dzieci z IgAN w grupach A i B oraz w grupie kontrolnej (K)

Group (Grupa)	A	B	K
Col IV 0	62.68 ± 90.55	27.96 ± 19.69	12.13 ± 4.6

A *vs.* B (ns.), A *vs.* K ($p < 0.01$), B *vs.* K ($p < 0.05$).

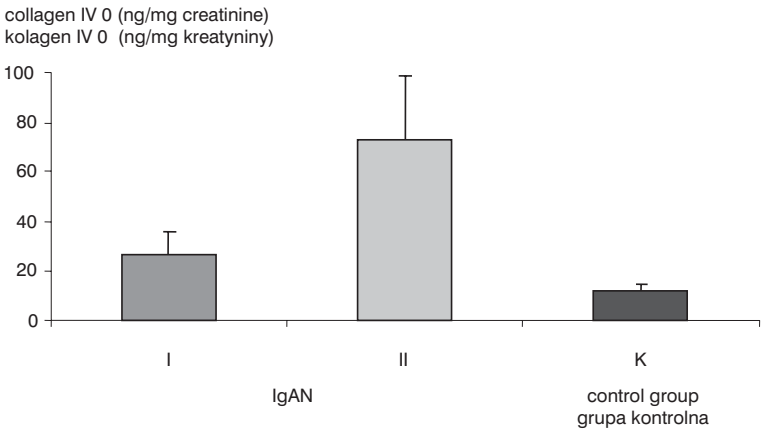

Fig. 2. Mean values of urine collagen IV in children with IgA nephropathy in groups I and II and in the control group at the onset of observation

Ryc. 2. Stężenie kolagenu IV na początku obserwacji w moczu dzieci z IgAN w grupach I i II w porównaniu z grupą kontrolną K

Group (Grupa)	I	II	K
Col IV 0	28.18 ± 21.02	75.44 ± 103.93	12.13 ± 4.6

I – with WHO grade I/II, II – with WHO grade III/IV, K – control group
I *vs.* II (ns., p = 0.06), I *vs.* K ($p < 0.01$), II *vs.* K ($p < 0.05$).

I – grupa z I/II stopniem wg WHO, II – grupa z III/IV stopniem wg WHO, K – grupa kontrolna
I *vs.* II (ns., p = 0,06), I *vs.* K ($p < 0,01$), II *vs.* K ($p < 0,05$).

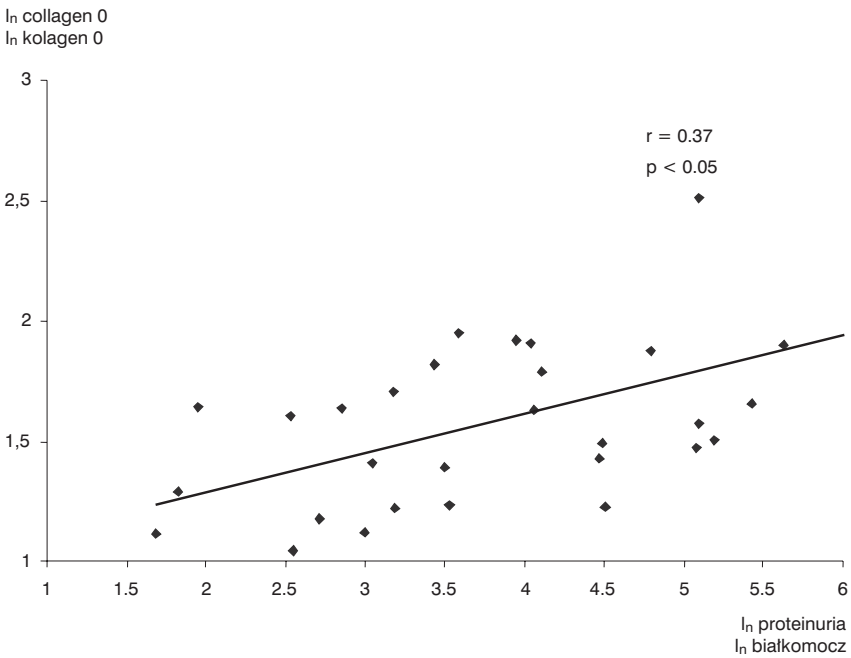

Fig. 3. Correlation between collagen IV at the onset of observation and proteinuria at the onset of illness in children with IgAN

Ryc. 3. Zależność stężenia kolagenu IV na początku obserwacji od białkomoczu na początku choroby u dzieci z IgAN

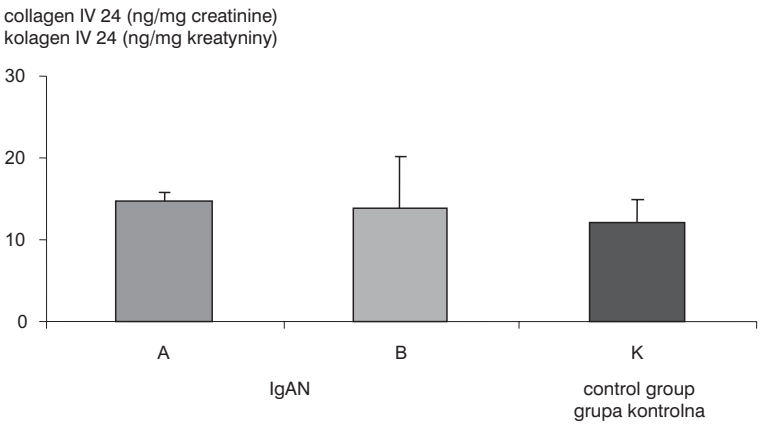

Fig. 4. Mean values of urine collagen IV in children with IgA nephropathy in groups A and B and in the control group at the end of observation

Ryc. 4. Średnie wartości stężenia kolagenu IV w moczu na zakończenie obserwacji u dzieci z IgAN w grupach A i B oraz w grupie kontrolnej (K)

Group (Grupa)	A	B	K
Col IV 0	14.85 ± 6.98	13.94 ± 9.75	12.13 ± 4.6

A *vs.* B (ns.), A *vs.* K ($p < 0.01$), B *vs.* K ($p < 0.05$).

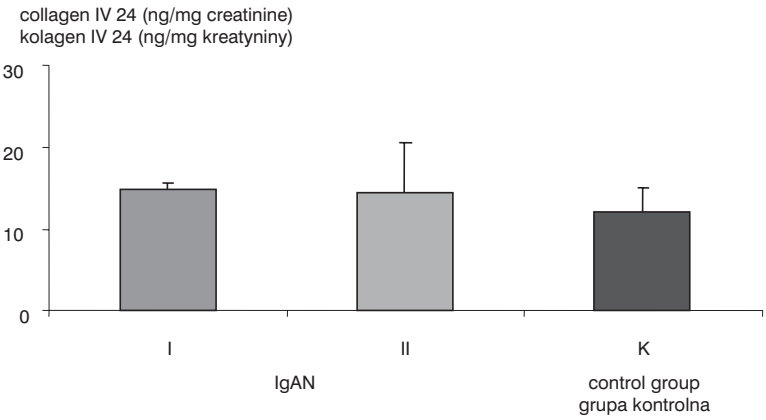

Fig. 5. Mean values of urine collagen IV in children with IgA nephropathy in groups I and II and in the control group at the end of observation

Ryc. 5. Średnie wartości stężenia kolagenu IV w moczu na zakończenie obserwacji u dzieci z IgAN w grupach I i II oraz w grupie kontrolnej (K)

Group (Grupa)	I	II	K
Col IV 0	14.69 ± 8.34	14.43 ± 7.59	12.13 ± 4.6

I *vs.* II (ns.), I *vs.* K ($p < 0.01$), II *vs.* K ($p < 0.05$).

histological severity of renal lesions at baseline. The mean urinary Col IV 24 level was insignificantly higher in patients with IgAN than in the control group. Mean Col IV 24 values in groups A (with proteinuria) and B (without proteinuria) and in the control group are shown in Figure 4. At 24 months, the mean urinary Col IV level in patients with IgAN was insignificantly higher in group A than in group B and it did not differ significantly from the mean urinary Col IV level in the control group.

Finally, the mean urinary Col IV 24 level in the children with IgAN and WHO grades I–II renal lesions was insignificantly higher than in children with WHO grades III–IV renal lesions. Mean Col IV 24 values in groups I and II did not differ significantly from the mean urinary Col IV level in the control group (Fig. 5).

Discussion

Baseline urinary Col IV excretion in the children with IgAN of the present study was significantly higher than in the control group ($p < 0.05$), which is in line with observations of other authors who showed higher collagen levels in patients with glomerulonephritis compared with controls [17]. Among the children with IgAN were insignificantly higher urinary Col IV levels at baseline in patients with proteinuria than in patients without proteinuria. A positive correlation ($r = 0.37$, $p < 0.05$) was also found between baseline collagen level and the severity of proteinuria at baseline in the patients with IgAN, which may be related to an increased severity of the inflammatory process in patients with proteinuria. Insignificantly higher urinary Col IV levels at baseline in children with more severe changes in the renal biopsy (WHO grade III–IV renal lesions) compared with children

with WHO grade I–II renal lesions may confirm the presence of tubulointerstitial changes and are consistent with results obtained by other authors who reported Col IV accumulation within the damaged interstitium and renal tubules [10, 14–16]. At 24 months a significant decrease in the mean urinary Col IV level was found in the patients with IgAN of the present study, resulting in an insignificant difference compared with the control group, which may represent an effect of the treatment administered in these patients. Finally, there was a negative correlation between baseline urinary collagen level in the patients of the present study and their age at the onset of the disease ($r = –0.47$, $p < 0.01$), indicating a more severe initial course of the disease in younger children.

The authors conclude that the dynamic changes in urinary Col IV level seen in the children with IgAN and its positive correlation with the presence of proteinuria in the course of the disease suggest that determination of urinary Col IV excretion may be a useful marker of the activity of nephropathy.

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Conflict of interest: None declared

Received: 20.12.2007
Revised: 25.01.2008
Accepted: 20.03.2008