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Is adiponectin in children with immunoglobulin A vasculitis a suitable biomarker of nephritis in the course of the disease?

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Abstract

Introduction: Immunoglobulin A vasculitis (IgAV) is the most common form of vasculitis in children. Nephritis in the course of this disease (IgAVN) is observed in 30–50% of patients and might lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Finding a non-invasive biomarker to distinguish initially between patients with and without nephritis and to facilitate a therapeutic decision to reduce the risk of long-term renal impairment is currently the target of much research. The aim of this study was to evaluate the adiponectin concentration in children with IgAV and estimate whether it might be used as a marker of IgAVN.

Material and methods: The study involved 29 IgAV children and 34 healthy controls. Eleven (38%) patients had renal involvement (IgAV-N) and 18 (62%) did not exhibit nephritis (IgAV-noN). The serum adiponectin level was estimated in children in an acute phase of IgAV and after 2–6 months during a follow-up visit. The relationship between the concentration of adiponectin and anthropometric measurements, epidemiological data and laboratory parameters were evaluated.

Results: The concentration of adiponectin in serum was significantly higher in children with acute phase of IgAV as compared to the control group ($p < 0.001$), and in patients without renal involvement in comparison with IgAV-N children ($p < 0.049$). In analysis of correlation we found a negative relationship between adiponectin level and serum creatinine concentration ($r = –0.437$, $p = 0.02$). The logistic regression evaluation demonstrated that a low adiponectin level increased the risk of nephritis in the course of IgAV.

Conclusions: Our study revealed that the serum adiponectin level increased markedly in patients with IgAV. We also documented that higher risk of nephritis in the course of the disease was associated with lower concentration of this hormone. **(Endokrynol Pol 2020; 71 (6): 512–517)**

Key words: *IgA vasculitis; nephritis; children; adiponectin*

Introduction

Immunoglobulin A vasculitis (IgAV), previously reported as Henoch-Schönlein Purpura (HSP), is the most common form of vasculitis in children, with an annual incidence estimated at 3–26.7/100,000/year [1]. The most typical symptom of IgAV is skin involvement, mainly presenting as a palpable purpura, which is often associated with systemic manifestations, including gastrointestinal pain and bleeding, arthralgia and/or arthritis, and glomerulonephritis. Although most symptoms are mild and self-limiting, renal involvement, which is observed in 30–50% of children in the course of the disease, is the most likely to result in long-term morbidity and mortality [2].

It is unknown why only some patients with IgAV experience renal injury. In recent years the target of much research was to find novel non-invasive biomarkers for the prediction of nephritis in the course of this disease.

Taking into account that the main cause of IgAV is small vessels inflammation we decided to evaluate adiponectin concentration in children suffering from this disease. Encouraged by the latest promising reports suggesting the role of this hormone in preventing inflammation and sclerosis in IgAN patients [3–5], we also tried to estimate whether its concentration is associated with renal involvement and if it is able to initially distinguish patients with higher risk of developing nephritis.

Material and methods

The study group comprised 29 children with IgAV. Diagnosis of the disease was based on the EULAR/PRINTO/PRES criteria [6]. Renal involvement was defined as the presence of haematuria: > 5 erythrocytes/high-power field and/or proteinuria: > 30 mg/mmol of urine protein/creatinine ratio (UP/UC ratio) and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.

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Thirty-four children hospitalised for nocturnal enuresis or presenting with procedures of one-day surgery were included into the control group matched in terms of age and gender to the study group. All children enrolled into the study were in stable clinical condition, proven by medical history, physical examination, and performed basic laboratory tests results. The patients with immunological diseases, symptoms of current infection, or incorrect laboratory test results were excluded from the controls.
The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (Resolution No. KNW/022/KB1/128/16), and written consent was obtained from parents or legal guardians, and/or patients.

Laboratory assays

Blood samples for laboratory tests from patients belonging to the study group were collected during the first few days after the patient's admission to the hospital in an acute phase of IgAV and after 2–6 months during a follow-up visit in a kidney outpatient clinic. Determination of adiponectin concentration was performed using ELISA kits (TECOmedical AG, Switzerland) according to the manufacturer's protocol.

Statistical analysis

All statistical analyses were performed using licensed version 10.0 software Statistica (StartSoft Inc., USA). For all parameters, the normality of distribution was determined by the Shapiro-Wilk test. For comparisons of variables with normal distribution Student's t-test was used. The non-parametric Mann-Whitney U-test was used for comparisons of parameters with distribution diverged from the normal one. Correlations were analysed with Spearman test. To analyse associations between quantitative variables Pearson's chi-squared test was performed. Logistic regression analysis was used to assess the usefulness of evaluating adiponectin in detecting nephrological complications in the course of the disease. $p<0.05$ was considered significant.

Results

The children from the study and control group did not differ significantly in terms of anthropometric and blood pressure measurements (Tab. 1).

Characteristics of IgAV patients at inclusion

In our study group 11 (37.9%) patients had renal involvement (IgAV-N) and 18 (62.1%) did not exhibit nephritis (IgAV-noN). In patients with diagnosed IgAV we observed male predominance (58.6% *vs*. 41.4%); however, it was more pronounced in children from the IgAV-N group (90.9% *vs*. 9.1%, $p = 0.006$) (Tab. 1). The IgAV-N patients had significantly higher concentrations of creatinine ($p = 0.048$) and lower values of eGFR ($p = 0.004$) than children from the IgAV-noN group (Tab. 2).

Comparison of adiponectin concentrations in IgAV and control group patients

The concentration of adiponectin in serum was significantly higher in children with acute phase of IgAV as compared to the control group ($p < 0.001$) (Fig. 1). More-

Table 1. *Demographic characteristics of children with immunoglobulin A vasculitis at inclusion and children from the control group*

Parameters	IgAV group			Control group (n = 34)
	IgAV total (n = 29)	IgAV–N (n = 11)	IgAV–noN (n = 18)	
Gender M/F	17/12	10/1*	7/11	23/11
Age [years] [median (IQR)]	7.5 (6–10)	9.0 (6.0–13.5)	7.0 (6.0–8.0)	7.5 (6.0–13.0)
Height [cm] [median (IQR)]	125.0 (120–145)	143.0 (123.3–158.0)	124.5 (118.5–127.8)	134.5 (121.0–162.0)
Weight [kg] [median (IQR)]	27.7 (20.0–45.7)	45.5 (26.7–55.2)	23.7 (19.6–32.0)	26.5 (21.3–55.0)
BMI [kg/m^2] [median (IQR)]	17.2 (15.2–22)	20.7 (17.5–22.1)	16.4 (14.5–19.7)	16.5 (14.6–19.8)
SBP [mm Hg] [mean ± SD]	110.6 ± 13.3	113.4 ± 13.2	108.5 ± 13.4	114.3 ± 12.1
DBP [mm Hg] [mean ± SD]	68.7 ± 9.2	69.2 ± 5.4	68.3 ± 11.6	71.1 ± 10.3
MAP [mm Hg] [mean ± SD]	82.7 ± 9.1	83.9 ± 6.3	81.7 ± 11.0	85.5 ± 9.0

IgAV-N — patients with IgAV and nephritis; IgAV-noN — patients with IgAV and without nephritis; IQR — interquartile range; SD — standard deviation; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; MAP — mean arterial pressure; *$p < 0.05$ boys from IgAV-N group *vs*. girls from IgAV-noN group

Table 2. *Clinical characteristics and selected biochemical parameters of children with immunoglobulin A vasculitis at inclusion*

Parameter	IgAV total (n = 29)	IgAV-N (n = 11)	IgAV-noN (n = 18)
Clinical characteristics			
Skin involvement, n (%)	29 (100%)	11 (100%)	18 (100%)
Joint involvement, n (%)	15 (51.7%)	4 (36.4%)	11 (61.1%)
Gastrointestinal involvement, n (%)	19 (58.6%)	7 (63.6%)	10 (55.6%)
Renal involvement, n (%)	11 (37.9%)	11 (100%)	0 (0%)
Haematuria, n (%)	11(37.9%)	11 (100%)	0 (0%)
Proteinuria, n (%)	8 (27.6%)	8 (72.7%)	0 (0%)
Haematuria and proteinuria, n (%)	8 (27.6%)	8 (72.7%)	0 (0%)
Hypertension, n (%)	2 (6.9%)	2(18.8%)	0 (0%)
eGFR < 60 mL/min/1.72 m^2, n (%)	1 (3.4%)	1 (9.1%)	0 (0%)
Laboratory parameters			
HGB [g/dL] [mean ± SD]	13.5 ± 1.2	14.0 ± 1.1	13.2 ± 1.2
WBC [×10^3/μL] [mean ± SD]	11.4 ± 3.4	11.2 ± 4.0	11.6 ± 3.0
PLT [×10^3/μL] [mean ± SD]	391.6 ± 109.7	388.8 ± 96.6	393.3 ± 119.6
IgA [g/L] [median (IQR)]	1.8 (1.5–2.4)	2.1 (1.8–2.6)	1.7 (1.0–2.4)
Serum creatinine [μmol/L]	41.0	48.0	39.0
[median (IQR)]	(35.0–51.0)	(38.0–67.0)**	(31.0–46.0)
eGFR [mL/min/1.73 m^2]	112.4	94.3	117.4
[median (IQR)]	(94.7–121.3)	(86.8–102.4)*	(111.3–128.0)
Serum urea [mmol/l] [mean ± SD]	3.9 ± 1.3	4.3 ± 1.7	3.6 ± 1.1
Serum uric acid [μmol/l] [mean ± SD]	203.9 ± 42.8	208.4 ± 47.6	188.0 ± 19.8

eGFR — estimated glomerular filtration rate; HGB — haemoglobin level; WBC — white blood count; PLT — platelet count; *p < 0.005 IgAV-N *vs*. IgAV-noN; **p < 0.05 IgAV-N vs. IgAV-noN

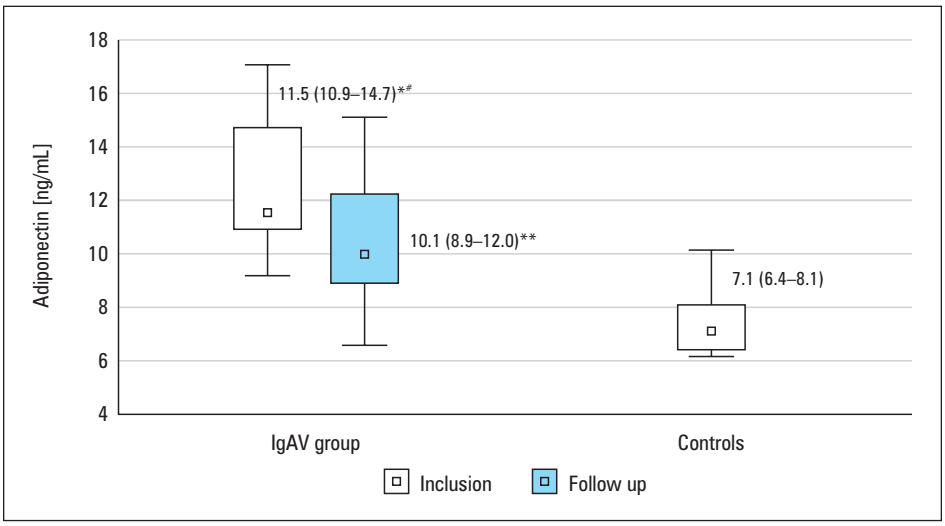

Figure 1. *Comparison between the concentration of serum adiponectin in children with immunoglobulin A vasculitis and patients from the control group. *p < 0.005 serum adiponectin level in IgAV group at inclusion vs. control group. #p < 0.005 serum adiponectin level in IgAV group at inclusion vs. values at follow-up. **p < 0.05 serum adiponectin level in IgAV group at follow-up vs. control group*

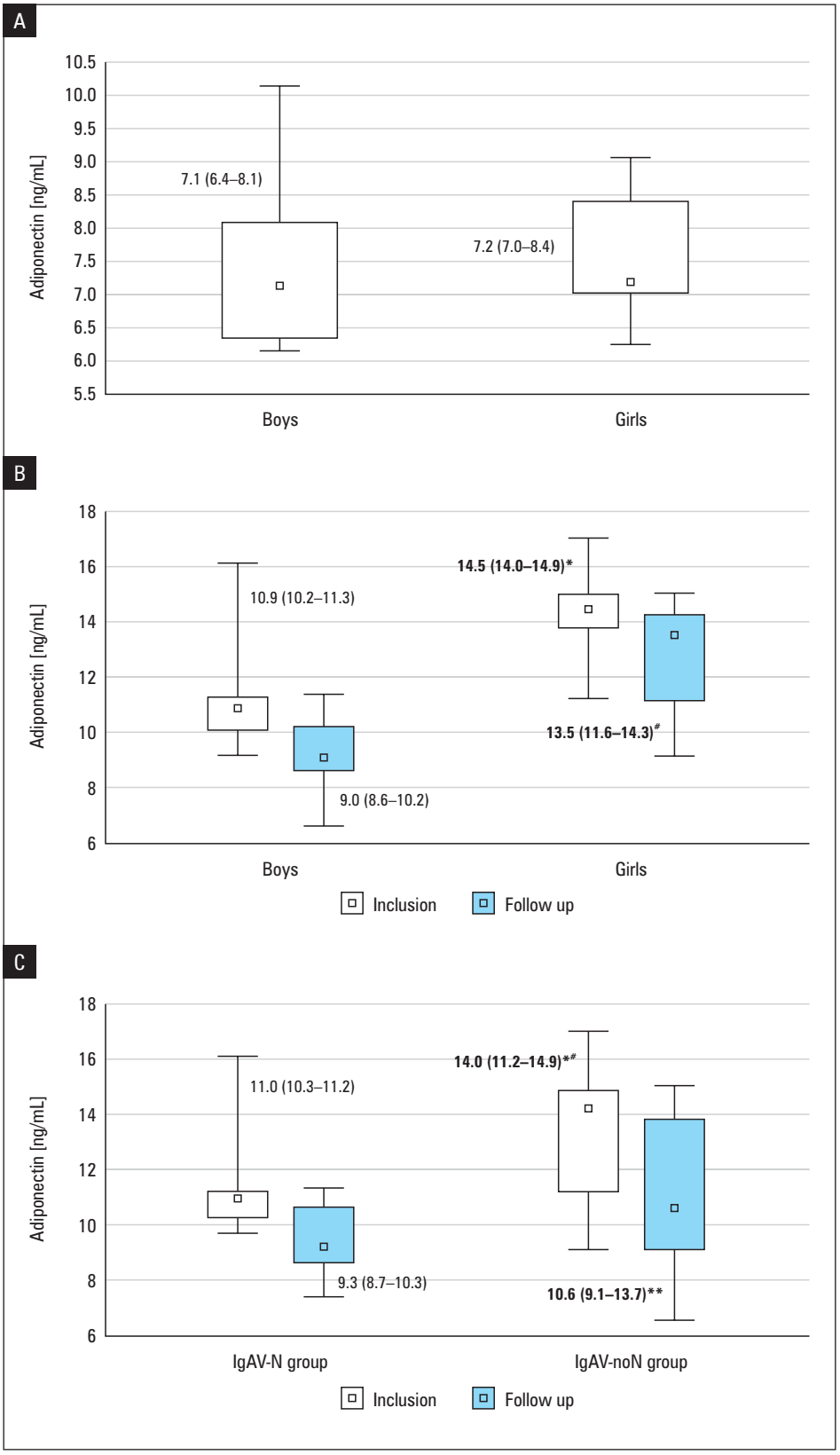

Figure 2. *Comparison between concentrations of serum adiponectin.* **A.** *In girls and boys from the control group ($p > 0.5$ serum adiponectin level in boys vs. girls from the control group);* **B.** *In girls and boys with IgAV (*$p < 0.005$ serum adiponectin level at inclusion in girls vs. boys with IgAV, #$p < 0.05$ serum adiponectin level at follow-up in girls vs. boys with IgAV);* **C.** *In children from IgAV-N and IgAV-noN groups (*$p < 0.05$ serum adiponectin level in IgAV-noN vs. IgAV-N group at inclusion, #$p < 0.005$ serum adiponectin level in IgAV-noN at inclusion vs. values at follow-up,**$p < 0.005$ serum adiponectin level in IgAV-noN vs. IgAV-N group at follow-up*

over, it was significantly higher in IgAV girls ($p = 0.047$) and in the IgAV-noN group ($p = 0.049$) (Fig. 2).

Logistic regression analysis for possible risk factors of renal involvement in the course of IgAV

Logistic regression analysis in the univariate model of adiponectin and renal involvement in the course of IgAV showed that a higher risk of nephritis was associated with lower concentration of this hormone ($p = 0.042$).

Characteristics of IgAV patients at follow-up

After six months one child (3.4%) was lost to follow-up. No child developed de novo renal involvement or renal failure. The renal prognosis in most patients was good; only one (9.1%) still presented nephrotic range proteinuria. Eight (72.7%) children had haematuria, four (36.4%) had albuminuria, and one (9.1%) had haematuria and proteinuria. All children had normal eGFR.

Concentration of adiponectin in IgAV patients at follow-up and comparison of these results with values obtained at inclusion

In all IgAV patients the concentration of adiponectin was significantly lower at follow-up compared to the levels obtained at inclusion ($p < 0.001$). In addition, the values were still significantly higher in comparison to the control group ($p < 0.05$) (Fig. 1). Only in children from the IgAV-N group was the concentration of adiponectin in serum not changed significantly after several months, and it remained markedly lower than in children without nephritis ($p < 0.005$) (Fig. 2C).

Correlations between adiponectin concentration and age, results of anthropometric measurements, and biochemical parameters

Analysis of correlation showed that the adiponectin concentration obtained at the acute phase of IgAV had an association with nephritis, which presented as a negative correlation with serum creatinine concentration ($r = –0.437$, $p = 0.02$).

Discussion

Our study is the first to estimate the expression of adiponectin in children with IgAV. Adiponectin as a vascular-protective and anti-inflammatory hormone is the focus of many researchers currently. Initially it was thought to be synthesised exclusively by adipocytes; however, recent studies have shown that it is also expressed by other cell types including kidney mesangial cells [3]. As an anti-inflammatory protein it enhances the production of nitric oxide, reduces formation of reactive oxygen species in human neutrophils, inhibits monocyte adhesion, and stimulates anti-inflammatory interleukin 10 (IL-10) production by macrophages [7, 8]. Increased serum levels of adiponectin were found in single studies conducted on patients with several inflammatory diseases such as rheumatoid arthritis [9], cystic fibrosis (CF) [10], inflammatory bowel diseases (IBD) [11], and lupus nephritis [12]. However, the exact reason for the high observed adiponectin concentration in these diseases is not evident. Moreover, the results of other studies carried out in patients with CF and IBD did not confirm the above observations [13–14].

We showed that patients with IgAV had significantly higher concentrations of adiponectin in serum in comparison with the control group. Therefore, the main reason of IgAV is small vessel inflammation we propose that this observation may result from the role of adiponectin in modulating the inflammatory response. In several previously published studies the authors reported that the endothelial function was closely related to plasma adiponectin level and was impaired in hypoadiponectinaemia [15, 16].

Additionally, we revealed markedly higher levels of adiponectin in children without renal involvement compared to those with nephritis. In an analysis of the correlation we found a negative relationship between adiponectin level and serum creatinine concentration. Further investigation demonstrated that a low adiponectin level increased the risk of nephritis in the course of IgAV. We hypothesise that this finding may be connected with the protective role of this hormone on the kidneys. As was revealed by other researchers, adiponectin not only modulates the process of inflammation and oxidative stress in kidneys but also alters podocyte function [17–20].

Our assumptions are confirmed by studies conducted on patients with IgA nephropathy (IgAN), which documented that lower adiponectin concentration promotes inflammation and sclerosis in this disease [3–5]. Previously, Uchida et al. evaluated the effect of glucocorticoid pulse therapy on adiponectin concentration in adult patients with IgAN and revealed that after this therapy the plasma adiponectin levels increased [4]. Subsequently, Iwasa et al. proved that serum adiponectin level was an independent determinant of arteriosclerosis in IgAN adult patients and suggested that this hormone may prevent renal arteriosclerosis [5]. Finally, Inoue et al. revealed that secretion of adiponectin in human mesangial cells was suppressed after stimulation by aberrantly glycosylated IgA1. What is more, the authors observed a downregulation of adiponectin expression in the glomeruli in kidney biopsy specimens from patients with IgAN [3]. Because the pathogenic mechanisms of renal involvement in IgAV and IgAN are

supposed to be identical, the data presented above seem to be the best for comparison with our observations.

We also documented a significant male predominance in the group with nephritis, which was reported previously and is considered as a risk factor for renal involvement in the course of IgAV [21]. In connection with the fact that the serum adiponectin level is even two-fold higher in females than in males [22], we compared its concentration between genders in study and control groups and revealed significant differences only in the IgAV group. This observation suggests that in healthy children adiponectin levels are comparable between genders and only during disease do their lower concentrations in boys become significant. However, whether the male gender is a risk factor for nephritis due to the lower potential for adiponectin increase during IgAV requires further investigation.

After the follow-up period we demonstrated significantly lower adiponectin levels in all patients from the study group in comparison with the value obtained at inclusion. However, only in children with renal complications were the adiponectin levels not markedly decreased. This observation might be connected with the fact that most of them still presented nephrological complications.

A limitation of our study was the relatively small sample size and also the mild character of kidney involvement. However, in a single-centre research it is difficult to collect a more numerous study group of children because the course of IgAV is mostly benign and serious kidney complications are very rare. Another limitation is the gender distribution with male predominance in the study group, but, as was previously noted, this is related to the characteristics of the disease.

Conclusions

Our study revealed that serum adiponectin levels increased significantly in patients with IgAV. What is more important, we documented that higher risk of nephritis in the course of the disease was associated with lower concentration of this hormone. Due to anti-inflammatory and kidney protective functions of adiponectin, our observations suggest its potential role in the prevention of renal injury in the course of IgAV. However, because the above observations are herein first described in the literature, there is a need to conduct further large scale multi-centre clinical studies to confirm these results.

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