jraas

Journal of the Renin-Angiotensin-Aldosterone System
April-June 2016: 1–7

DOI: 10.1177/1470320316647240
jra.sagepub.com
SAGE

Plasma oxidative stress level of IgA nephropathy in children and the effect of early intervention with angiotensin-converting enzyme inhibitors

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Abstract

Aim: The purpose of this study was to investigate the change of the plasma oxidative stress level in children with IgA nephropathy (IgAN) and analyze its relativity to the clinical and pathological classification. To discuss the early effects of angiotensin-converting enzyme inhibitors (ACEIs) on the plasma oxidative stress level in children with IgA nephropathy.

Methods: Thirty-eight children with IgAN were divided into groups according to their clinical features, pathologic grades, and treatments. Twenty healthy children were included in the control group.

Results: The plasma level of advanced oxidation protein products (AOPPs), malonaldehyde (MDA), and superoxide dismutase (SOD) were detected. The plasma level of oxidative stress was significantly increased in the IgAN group, including a higher plasma level of AOPP and MDA and a lower plasma level of SOD. After treatment, the plasma level of oxidative stress was significantly decreased in the ACEI group.

Conclusions: The children with IgAN had an increase in the plasma level of oxidative stress, expressed as an increased plasma level of AOPP and MDA and a decreased plasma level of SOD. Oxidative stress was associated with the progression of IgAN in children. Early treatment with ACEI therapy can significantly reduce the plasma level of oxidative stress in children with IgAN.

Keywords

IgA nephropathy, oxidative stress, angiotensin converting enzyme inhibitor, glomerulonephritis, children

Date received: 6 January 2016; accepted: 29 February 2016

Introduction

IgA nephropathy (IgAN) is the most common primary glomerular disease in children, and its pathogenesis has not been fully elucidated. A study with a 20-year follow-up shows that 30% of patients with childhood IgAN developed end-stage renal disease (ESRD).[1,2] Angiotensin-converting enzyme inhibitors (ACEIs) are one of the recognized medications for delaying the progression of nephropathy through a mechanism that is not related to blood pressure effects.[3–8] Over a decade ago, it was observed that angiotensin II (Ang II) can activate NADPH oxidase that mediates reactive oxygen species (ROS) production.[9,10] It has been clinically demonstrated that the immunoreactivities of intrarenal heme oxygenase-1 (HO-1) and 4-hydroxy-2-nonenal (4-HNE) (markers of ROS) and those of intrarenal angiotensinogen (AGT) and angiotensin II (Ang II) (markers of the renin angiotensin system (RAS)) in IgA nephropathy patients were significantly increased compared to those of control subjects. Moreover, an interventional study using high IgA (HIGA) mice demonstrated that the expressions of two lines of

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intrarenal ROS markers (4-HNE and HO-1), two lines of intrarenal RAS markers (AGT and Ang II) and renal damage decreased significantly in HIGA mice receiving treatment with the Ang II receptor blocker olmesartan but not in HIGA mice receiving treatment with RAS-independent antihypertensive drugs (hydralazine, reserpine, and hydrochlorothiazide) when compared with HIGA mice that were not treated. These data suggest that intrarenal ROS and RAS activation plays a pivotal role in the development of IgA nephropathy.[11] Oxidative stress refers to an imbalance in oxidants and antioxidants, causing oxidative damage to cells and tissues. Recent studies have shown that there are increased oxidative stress levels in the plasma and kidneys in adult patients with IgAN. Antioxidant therapy can delay renal failure in adult patients with IgAN, showing that oxidative stress is involved in IgAN pathogenesis.[12–14] However, there are no reports that demonstrate changes in the plasma oxidative stress levels in children with IgAN or whether ACEIs can affect plasma oxidative stress levels in children with IgAN. This study investigates the plasma oxidative stress level in children with IgAN, compares the relationship to clinical pathology, and presents the influence of ACEIs on oxidative stress by testing advanced oxidation protein products (AOPPs), malonaldehyde (MDA) and superoxide dismutase (SOD) levels.

Materials and methods

Clinical data

From November 2010–November 2012, 44 cases of children with primary IgAN were diagnosed by light microscopy, immunofluorescence, and electron microscopy in the Pediatric Nephrology Center of the Department of Pediatrics in the First Affiliated Hospital of Sun Yat-sen University. We excluded two cases that received previous ACEI or angiotensin receptor blocker (ARB) treatments, three cases of reduced glutathione treatments and one case of severe infection, leaving 38 cases with pediatric IgAN. Twenty-seven of these patients were males and 11 were females. The ages of 38 children visited their physician range from 6 years and 5 months to 11 years. 'The median patient age was nine years and one month. The duration from initial visit to confirmed diagnosis ranged from 29 days to three months. The patients' kidney function tests were normal. Meanwhile, we performed a physical examination on 20 healthy children as the control group that were matched for age and gender with the IgAN patients. The control group children had no medication histories or a history of infection within the past three months. This study was approved by the ethics committee of The First Affiliated Hospital of Sun Yat-sen University and has therefore been performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. All of the children's parents signed informed consent before participating.

Inclusion and exclusion criteria

1. Children with ages ranging from 0–14 years were included.
2. According to the diagnostic standard of primary IgAN in children, immune globulin deposition, mainly with IgA, in the glomerular mesangial area and/or capillary loops is present; however, diseases in which IgA is deposited in the kidney, such as Henoch-Schönlein purpura (HSP), systemic lupus erythematosus (SLE), and chronic liver diseases, do not meet the standard.
3. Children with tumors, infections, acute cardiovascular events, active bleeding, and a history of a blood transfusion within one month of initiation of this study were excluded.
4. Children who had received antioxidant treatments, such as vitamin C, vitamin E and reduced glutathione, within one month of the initiation of this study were excluded.
5. Children who had received ACEI and ARB treatments were excluded.
6. Children who had other primary glomerular diseases or renal tubulo-interstitial lesions caused by drugs and metabolism were excluded.

Case mix group

According to the 2001 standard developed by The Subspecialty Group of Nephrology, the Society of Pediatrics, Chinese Medical Association,[7] children with IgAN were divided into three groups based on clinical manifestations: 14 cases in the hematuria and proteinuria (HP) group, seven cases in the acute glomerular nephritis (AGN) group and 17 cases in the nephrotic syndrome (NS) group. HP is characterized by proteinuria and microscopic hematuria or gross hematuria and 24 h urine protein (Upro) that is less than 50 mg/kg. AGN is characterized by proteinuria, hematuria with or without hypertension or acute renal failure. NS is defined as proteinuria, hypoalbuminemia with or without hypercholesterolemia and edema.

According to the World Health Organization (WHO) pathological classification standard,[4,7,15,16] children with IgAN were divided into three groups: 22 cases in the pathology III group, 10 cases in the pathology IV group and six cases in the pathology V group. Based on whether patients received hormone and immunosuppressant therapy after diagnosis in our hospital, children with IgAN were categorized into a primary group with 28 cases and a non-primary group with 10 cases. The primary group consisted of two sub-groups: an ACEI group (n=10) and a non-ACEI group (n=18). Subjects in the former group were diagnosed with hypertension, were being treated with glucocorticoids and/or immune-suppressants according to their clinical classification and pathologic

Table 1. The clinical classification, pathological grade and treatment plan in the angiotensin-converting enzyme inhibitor (ACEI) group and non-ACEI group of IgA nephropathy (IgAN) children.

Group	Case	Clinical classification			Pathological grade			Treatment	
		HP	AGN	NS	III	IV	V	MP	MP+CTX
ACEI group	10	1	7	2	8	2	0	4	6
Non-ACEI group	18	13	0	5	14	4	0	8	10

AGN: acute glomerular nephritis; CTX: cyclophosphamide; HP: hematuria and proteinuria; MP: methylprednisolone; NS: nephrotic syndrome.

grade and were taking ACEI drugs (fosinopril, 0.3–1 mg/kg.d once a day) at the beginning of treatment. The type and dosage of glucocorticoids and immune-suppressants can be found in the therapeutic schedule in 'Trial evidence-based guidelines of common kidney disease in children (IV) in 2010'.[7] Subjects in the non-ACEI group were not diagnosed with hypertension but were treated with glucocorticoids and/or immune-suppressants according to their clinical classification and pathologic grade (Table 1).

Serological tests

All samples were taken after fasting using a drying tube to collect 2 ml of peripheral venous blood. Plasma was separated within 30 min of collection (4°C low-temperature plasma separation for 15 min, 3000 r/min, r=20 cm). These samples were stored in a −80°C freezer and analyzed within six months. Additionally, we used separation gel tubes to collect 2 ml of peripheral blood and isolated the serum (3500 r/min, centrifugal separation for 10 min) after storage at room temperature for 30 min. After five months of treatment, children in the primary group required repeated blood collection. AOPP, MDA and SOD levels in the drying tubes were measured by the Wikto-sarsat spectrophotometric method,[17] thiobarbituric acid spectrophotometric method and xanthine oxidase technique, respectively. Blood urea nitrogen (BUN), serum creatinine (Scr) and serum cystatin C (Cys-C) levels were detected by a 7170A automatic biochemical analyzer. All the kits were purchased from Nanjing Jiancheng Bioengineering Institute.

Urine tests

We collected 24-hour urine specimens one day prior to blood collection and recorded the exact volume with graduated cylinders. After sufficient mixing, we took 15 ml of urine to measure 24-hour urine protein and β2 microglobulin (β2-MG) levels in urine using the sulfosalicylic acid method and electrochemiluminescence method, respectively. The 24-hour proteinuria was adjusted to body surface area (BSA) according to Chinese guidelines. Creatinine clearance rate (Ccr) in ml/1.73 m^2.min was measured by the following formula

$$Ccr=24\ Ucr\times 700\times 1.73/Scr\times BSA$$

Renal pathological grading

Children with IgAN were scored according to the Katafuchi semi-quantitative criteria.[6]

Statistical analysis. SPSS 17.0 software was used for data analysis. Data were quantitatively represented using the mean and standard deviation ($\bar{x}\pm s$) or the median and inter-quartile range (M (Q_1-Q_3)), depending on the distribution of the data. The *t*-test or the rank-sum test were used to compare two groups of quantitative data depending on the distribution of the data. Pearson correlation analysis method or the Spearman rank correlation analysis method was used for correlation analysis between two groups, depending on the distribution of the data. Values of $p<0.05$ indicate statistical significance.

Results

Plasma levels of oxidative stress in children with IgAN

Compared with the control group, AOPP plasma level in the IgAN group was significantly increased ((99±27) vs (53±21) μmol/ml), MDA level was significantly increased ((5.3±2.1) vs (2.5±1.4) nmol/ml), and SOD level was significantly decreased ((67±21) vs (95±20) U/ml). Differences were statistically significant ($p<0.01$).

The plasma levels of oxidative stress indicators in the NS group are the highest among all clinical classification groups (Table 2). Whereas, the plasma levels of oxidative stress indicators in pathology group V are the highest among all pathological groups (Table 3).

Correlation analysis between oxidative stress indicator levels and clinical indicators for children with IgAN

There was a positive correlation between oxidative stress indicator levels and serum Cys-C level and oxidative stress level and 24-hour urine protein level. In addition, a positive correlation was present between

Table 2. The plasma level of oxidative stress indicators between different IgA nephropathy (IgAN) clinical groups ($\bar{x}\pm s$).

	Control (n=20)	HP group (n=14)	AGN group (n=7)	NS group (n=17)
AOPP (μmol/ml)	53 ± 21	88 ± 20[a,b]	92 ± 2[a,b]	114 ± 26[a]
MDA (nmol/ml)	2.5 ± 1.4	4.2 ± 1.6[a,b]	4.4 ± 1.9[a,b]	6.6 ± 1.8[a]
SOD (U/ml)	95 ± 20	78 ± 19[a,b]	73 ± 18[a,b]	61 ± 18[a]

AGN: acute glomerular nephritis; AOPP: advanced oxidation protein product; HP: hematuria and proteinuria; MDA: malonaldehyde; NS: nephrotic syndrome; SOD: superoxide dismutase.
[a]Compared with control group, $p<0.05$; [b]compared with nephrotic syndrome (NS) group, $p<0.05$.

Table 3. The plasma level of oxidative stress between different IgA nephropathy (IgAN) pathological groups ($\bar{x}\pm s$).

	Control (n=20)	Grade III group (n=22)	Grade IV group (n=10)	Grade V group (n=6)
AOPP (μmol/ml)	53 ± 21	90 ± 21[a,b]	105 ± 20[a,b]	133 ± 19[a]
MDA (nmol/ml)	2.5 ± 1.4	5.0 ± 2.0[a,b]	5.1 ± 1.9[a,b]	6.9 ± 2.2[a]
SOD (U/ml)	95 ± 20	74 ± 18[a]	66 ± 22[a]	60 ± 21[a]

AOPP: advanced oxidation protein product; MDA: malonaldehyde; SOD: superoxide dismutase.
[a]Compared with control group, $p<0.05$; [b]compared with Grade V group, $p<0.05$.

Table 4. Relationship between clinical data and plasma oxidative stress level in IgA nephropathy (IgAN) children (r).

Index	BUN	SCr	Ccr	Cys-C	24 h Upro	Urine-β_2-MG	Urine TF
AOPP	0.395[a]	0.376[a]	0.304	0.630[b]	0.614[b]	0.372[a]	0.442[b]
MDA	0.343[a]	−0.158	0.002	0.483[b]	0.509[b]	0.105	0.146
SOD	−0.284	−0.156	0.212	−0.500[b]	−0.349[a]	−0.313[a]	−0.294[a]

AOPP: advanced oxidation protein product; BUN: blood urea nitrogen; Ccr: creatinine clearance rate; Cys-C: serum cystatin C; MAP: mean arterial pressure; MDA: malonaldehyde; SCr: serum creatinine; SOD: superoxide dismutase; Urine β_2-MG: urine β2 microglobulin; Upro: urine protein; Urine TF: urine transferrin.
[a]$p<0.05$; [b]$p<0.01$.

oxidative stress level and β2-MG level for children with IgAN (Table 4).

Correlation analysis between plasma oxidative stress indicator levels and the Katafuchi score in IgAN children

There were positive correlations between AOPP, MDA and the total renal lesion score and the renal tubulointerstitial lesion score in IgAN children. Correlations were not found between SOD and the total renal lesion score, renal tubulointerstitial lesion score, or renal vascular lesion score ($p>0.05$, Table 5).

Clinical data before and after treatment in the ACEI and non-ACEI groups, and the effects on plasma oxidative stress indicator levels in children with IgAN

Clinical data. Significant decreases in Upro values after five months of treatment were found in both the ACEI and non-ACEI groups (both are $p<0.05$); however, the degree of decline was not statistically significant between the two groups ($p>0.05$). BUN, Scr, Ccr, Cys-C, urine β_2-MG and urine transferrin (urine TF) value differences between before and after treatment were not statistically significant in the ACEI and non-ACEI groups ($p>0.05$, Table 6).

Plasma oxidative stress level. Before treatment, there were no significant differences in oxidative stress indicator levels between the ACEI and non-ACEI groups ($p>0.05$). After treatment, plasma oxidative stress indicator levels in the ACEI treatment group were significantly reduced ($p<0.05$), and the decrease in the ACEI group was significantly greater than in the non-ACEI treatment group ($p<0.05$, Figure 1, Table 7).

Discussions

Plasma oxidative stress indicator levels in IgAN children

Oxidative stress is the result of an imbalance between oxidants and the antioxidant defense system, leading to oxidative damage to tissues and cells with ROS. As ROS are rapidly metabolized and difficult to detect, oxidative stress

Table 5. Relationship between the Katafuchi score and plasma oxidative stress level on IgA nephropathy (IgAN) children (*r*).

Index	Total renal lesion score	Glomerular lesion score	Renal tubulointerstitial lesion score	Renal vascular lesion score
AOPP	0.480[a]	0.371	0.224	
MDA	0.324[a]	0.361	0.202	
SOD	−0.079	0.038	−0.072	

AOPP: advanced oxidation protein product; MDA: malonaldehyde; SOD: superoxide dismutase.
[a]$p<0.05$; [b]$p<0.01$.

Table 6. The clinical data before and after treatment between angiotensin-converting enzyme inhibitor (ACEI) group and non-ACEI group of IgA nephropathy (IgAN) children ($\bar{x} \pm s$, $M(Q_L–Q_U)$).

		ACEI group	Non-ACEI group
Case		10	18
Sex	Male	7	13
	Female	3	5
Median age (years)		9.2 (6.5–10.6)	8.6 (5.3–11.4)
Median disease course (day)		45 (26.5–77.5)	52 (32.6–75.0)
MAP (mm Hg)	Before	98 ± 16[a]	84 ± 22
	After	86 ± 13[b,c]	80 ± 26
Urine protein (mg/(kg.d))	Before	19.5 (14.1–51.1)	33.5 (10.6–58.6)
	After	9.7 (5.6–22.0)[b]	10.3 (6.8–17.6)[b]
BUN (mmol/l)	Before	6.2 ± 2.7	5.4 ± 1.8
	After	6.4 ± 1.9	6.2 ± 1.4
SCr (umol/l)	Before	55.6 ± 19.1	58.7 ± 23.9
	After	57.9 ± 22.3	62.3 ± 25.6
Ccr (ml/1.73 m^2/min)	Before	133.6 ± 44.9	128.3 ± 36.6
	After	130.4 ± 36.4	122.8 ± 42.3
Cys-C (mg/l)	Before	0.85 (0.75–0.95)	0.95 (0.84–1.02)
	After	0.84 (0.78–0.92)	0.96 (0.89–1.14)
Urine β_2-MG (mg/l)	Before	0.23 (0.22–0.24)	0.27 (0.22–0.43)
	After	0.24 (0.23–0.25)	0.27 (0.22–0.27)
Urine TF (mg/l)	Before	42.2 (8.9–68.9)	29.2 (26.6–83.5)
	After	43.8 (12.6–65.1)	30.6 (26.8–81.1)

BUN: blood urea nitrogen; Ccr: creatinine clearance rate; Cys-C: serum cystatin C; MAP: mean arterial pressure; SCr: serum creatinine; Urine β_2-MG: urine β2 microglobulin; Urine TF: urine transferrin.
[a]Compared with non-ACEI group, $p<0.05$; [b]compared with treatment before, $p<0.05$; [c]the value difference between before and after treatment compared with non-ACEI group, $p<0.05$.

levels are usually quantified by testing molecular markers of oxidative stress in a clinic. When the concentration of the products of oxidation reactions (such as AOPP and MDA) increases or when the activity of antioxidant enzymes (such as SOD) decreases, oxidative stress levels increase. This study reveals that when compared with a normal control group, plasma levels of AOPP and MDA are significantly increased and SOD level are decreased in IgAN children. In other words, oxidative stress levels are raised in children with IgAN, the results of which are consistent with animal experiments.[18] According to clinical and pathological analysis of IgAN children, results indicated that plasma oxidative stress levels in IgAN children had the highest value within the NS group and grade V group. AOPP, MDA, and SOD levels were strongly correlated with clinical and pathological classification. Thus, these results suggest that oxidative stress is involved in the pathogenesis of IgAN. IgAN children with more severe clinical manifestations had more significant pathological changes and higher plasma oxidative stress levels.

Renal fibrosis is a typical pathological change for IgAN children who progress to ESRD. Previous studies showed that oxidative stress is involved in the process of developing renal interstitial fibrosis.[19,20] In this study, there were positive correlations between AOPP and MDA levels in IgAN children and Katafuchi scoring. This result shows that renal fibrosis in children with IgAN may be caused by increased oxidative stress. On the other hand, a positive correlation was not observed between SOD levels in IgAN children and the Katafuchi scoring. The reason maybe that SOD is less sensitive in the early stages of renal injury, but in our study, the children did not clearly present with renal insufficiency.[21] Proteinuria is an independent risk factor for IgAN and can affect the prognosis.[22] According to the

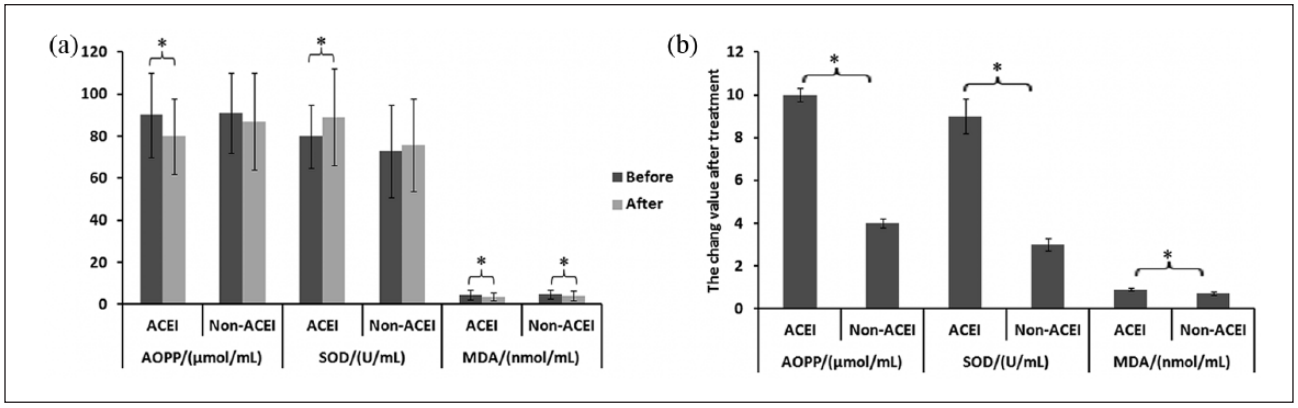

Figure 1. The plasma level of oxidative stress between different IgA nephropathy (IgAN) groups. After treatment, plasma oxidative stress indicator levels in the ACEI treatment group were significantly reduced (P<0.05) compared to treatment before (a), and the decrease in the ACEI group was significantly greater than the non-ACEI treatment group (P<0.05) (b). AOPP: advanced oxidation protein product; MDA: malonaldehyde; SOD: superoxide dismutase.

Table 7. The plasma level of oxidative stress indicators before and after treatment between angiotensin-converting enzyme inhibitor (ACEI) group and non-ACEI groups of IgA nephropathy (IgAN) children ($\bar{x}\pm s$).

Group	Case	AOPP (μmol/ml)		MDA (nmol/ml)		SOD (U/ml)	
		Before	After	Before	After	Before	After
ACEI group	10	90.4 ± 20.0	80.4 ± 17.5[a,b]	4.6 ± 2.3	3.7 ± 1.9[a,b]	80.4 ± 14.7	88.7 ± 23.4[a,b]
Non-ACEI group	18	90.6 ± 19.3	87.4 ± 22.6	4.9 ± 2.0	4.2 ± 2.3[a]	73.0 ± 22.2	75.6 ± 21.8

AOPP: advanced oxidation protein product; MDA: malonaldehyde; SOD: superoxide dismutase.
[a]Compared with the baseline before the treatment, $p<0.05$; [b]the change after treatment compared with non-ACEI group, $p<0.05$.

study results, 24-hour urine protein and oxidative stress levels were positively correlated. At this point, results were consistent with Tian and others.[23] Thus, oxidative stress may have a relationship with generating proteinuria in children with IgAN. Reducing oxidative stress in children with IgAN is a potential new treatment.

Cys-C is a sensitive indicator of the glomerular filtration rate[24] and can be used as an early predictive indicator of prognosis in patients with IgAN.[25] In this study, the results revealed that oxidative stress and Cys-C in children with IgAN were positively correlated; therefore, during follow-up, it is necessary to pay greater attention to renal function changes in IgAN children with increased oxidative stress.

Urine β_2-MG is a sensitive and specific indicator for renal tubular damage. Results from this study revealed that oxidative stress and urine β_2-MG in children with IgAN were positively correlated. Thus, oxidative stress may induce tubulointerstitial injury in IgAN children and can affect the pathogenesis and prognosis of the disease.

The influence of ACEI on oxidative stress in IgAN children

ACEIs are one of the accepted treatments for IgAN to delay progression to ESRD, especially for IgAN children with mild to moderate proteinuria.[7] However, the effective mechanism of action of ACEIs for IgAN is still unclear. Results in this study showed that the group treated with ACEIs had a significant decline in oxidative stress indicators AOPP and MDA and an increase in SOD. As a result, treatment with ACEIs can improve oxidative stress in IgAN children. A double-blind placebo-controlled experiment from the USA showed that treatment with antioxidant Vitamin E can improve oxidative stress in IgAN children;[26] meanwhile, 24-hour urine protein was significantly reduced, and the rate of decrease of glomerular filtration rate was delayed. Although both oxidative stress and urine protein levels for IgAN children in the ACEI group had an obvious decrease, there was no significant difference in decreased urine protein levels when compared with the non-ACEI group. Additionally, no change in renal function before and after treatments was observed in both groups. ACEIs can antagonize oxidative stress in IgAN, which may not be due to the decreasing of urine protein. Further study is required to determine the relationship between the antagonistic actions of ACEIs on oxidative stress and the mechanisms of renal protection. This study's limitations include the limited number of cases, short follow-up periods and normal renal function in most of the IgAN children. Only two children from the NS group had renal function damage (compensated), with creatinine clearance rates 62 and 73 ml/1.73 m^2/min,

respectively, but no significant impact on the other conclusions was found. The relationship between the antioxidant effect of ACEIs and the protection of renal function requires further research.

In conclusion, children with IgAN are under increased oxidative stress. Oxidative stress has a close relationship with existing clinical classifications, pathologic grading systems, and also relates to urine protein levels and the degree of renal interstitial fibrosis, all of which are important factors in IgAN pathogenesis and prognosis. ACEI medications can improve oxidative stress in children with IgAN.

Acknowledgements

The authors acknowledge technical assistance from the Department of Translational Medicine in the First Affiliated Hospital of Sun Yat-sen University.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Natural Science Foundation of Guangdong Province (grant number S2012010009335), the Science and Technology Program of Guangzhou, China (grant number 2014 A020212140), and the Traditional Chinese Medicine Bureau of Guangdong Province (grant number 20151161).

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