The Effect of α-Tocopherol on the Oxidative Stress and Antioxidants in Idiopathic IgA Nephropathy

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Objective: *Nearly 25% of IgA nephropathy patients progress to end-stage renal disease over a 20-25 year follow-up period. IgA containing immune complex stimulates oxygen free radical production by mesangial cells in vitro, which may mediate glomerular injury in this disorder. Therefore, we studied whether dietary supplementation with the antioxidant agent, vitamin E, attenuates renal damage in patients with IgA nephropathy.*
Material and Method: *Twenty-eight patients with idiopathic IgA nephropathy were supplemented with vitamin E 400 mg/day for 6 months. Antioxidant enzymes, glutathione, plasma malondialdehyde (MDA), and renal function were studied after 3 and 6 months therapy.*
Result: *The result of the study showed high plasma MDA and significant reduction after therapy (1.15 ± 0.45 VS 0.86 ± 0.30 μM, $p < 0.0001$). The RBC vitamin E was also elevated statistically significantly (5.07 ± 2.42 VS 15.70 ± 3.37 μM, $p < 0.001$). Glutathione peroxidase activities were decreased (38.52 ± 15.53 VS 23.97 ± 7.63 U/gHb, $p < 0.001$). Glutathione was also decreased (44.80 ± 9.70 VS 32.45 ± 6.74 mg/dl, $p < 0.05$) but there were no changes in red cell catalase and superoxide dismutase activities. Creatinine clearance, proteinuria, urine N-acetyl glucosaminidase and β_2-microglobulin also showed no improvement.*
Conclusion: *Our data demonstrated the particular group of IgA nephropathy patients with low vitamin E level and high oxidative stress had significant reduction of oxidative stress after vitamin E therapy.*

Keywords: *α-tocopherol, Antioxidants, IgA nephropathy, Oxidative stress*

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IgA nephropathy is among the most common primary glomerulonephritis in the world[1,2]. It accounts for 10-30% of all end stage renal diseases[3,4]. IgA nephropathy was originally considered a benign disorder that comprised minimal risk for the development of chronic renal failure. However, it is now accepted that renal failure develops in 20 to 40 percent of patients 5 to 25 years after diagnosis[5-7]. Characteristically, it presents with intermittent macroscopic hematuria in association with upper respiratory tract infection. The diagnosis is established by demonstrating predominant IgA deposits in the glomerular mesangium. The pathogenesis of IgA nephropathy remains unclear[1,2,8,9]. Being older, being male, and having hypertension, persistent proteinuria, impaired renal function at diagnosis, or glomerulosclerosis or interstitial fibrosis on renal biopsy are associated with more rapid progression of the disease[5-7,10]. There are no proven therapies that reverse the immunologic abnormalities or that consistently retard the course in those patients with IgA nephropathy who manifest progressive loss of kidney function[11].

Recent studies indicate that IgA -containing immune complexes stimulates production of oxygen free radicals by mesangial cells in situ[12]. Kashem et al[13] recently demonstrated significant superoxide pro-

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duction by polymorphonuclear leukocytes of patients with IgA nephropathy. The amount of free radical production correlated positively with the degree of proteinuria. Finally, aggregated IgA-induced Fcα receptor expression on polymorphonuclear leukocytes was positively correlated with superoxide anion production and the degree of proteinuria[13]. Thus, superoxide generation from IgA receptor-bearing polymorphonuclear leukocytes may contribute to the development of IgA nephropathy. The evidence of chronic effects of reactive oxygen intermediates on the kidney was also demonstrated by animal models using a dietary deficiency of selenium and vitamin E[14].

Vitamin E is a natural antioxidant and is not associated with any clinically relevant side effects in patients and in other contexts[15,16]. In the rat model of experimental IgA nephropathy, Trachtman et al in 1996[17] demonstrated increased renal gene expression of TGF-β_1 which was reversed by feeding with a vitamin E-supplemented diet. This is consistent with previous studies documenting an important role for TGF-β_1 in promoting intrarenal fibrosis and glomerulosclerosis in experimental kidney disease[18]. Oxidant stress therefore increases the renal activity of TGF-β_1, which augments glomerular scarring. Feeding with a vitamin E - enriched diet interrupts this process and protects against renal injury. Therefore, based on these experimental findings, we conducted a prospective non-placebo –controlled trial to study the effect of vitamin E in idiopathic IgA patients including oxidative stress, antioxidant enzymes and renal functions.

Material and Method

Fifty idiopathic IgA nephropathy patients proved by renal histopathology both from the out and inpatients of the Renal Division, Department of Medicine, Siriraj Hospital were enrolled in this study with informed consents. Exclusion criteria were patients with chronic respiratory insufficiency, intercurrent infection, hepatic disorders, alcoholics or smokers. None of them had received either blood or plasma during the 4 months preceding the study. Twenty-eight IgA patients who had high oxidative stress (MDA) or low vitamin E levels were administrated with α-tocopherol of 400 mg daily for 6 months. Thirty age-and sex matched volunteers from the hospital staff and personnel constituted normal, healthy controls.

Method

The following investigations were performed in all the study groups: Urinalysis, 24 hours for protein, creatinine clearance, serum creatinine, albumin, cholesterol, and triglycerides. Antioxidant enzymes were assayed: superoxide dismutase (SOD) using the Winterbourn CC et al method[19], glutathione (GSH), glutathione peroxidase (GSH-Px) and catalase by the Butler method[20,21,22]. Malondialdehyde (MDA) determination using the Hong YL method[23], and red blood cell vitamin E by high performance liquid chromatography[24]. β_2 – microglobulin and N - acetyl glucosaminidase were determined by enzymatic reaction assay[26,27].

Vitamin E treatment

Vitamin E capsule (α-tocopherol) was the product of Pfizer by R.P Scherer G M B H, Eberbach/ Baden, West Germany. Each capsule contained 100 milligrams. The patients were given vitamin E of 400 mg daily for 6 months, during which no immunosuppressive drug therapy or angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonist were administered during this period.

Analytical method

The patients were followed up clinically every month. No side effects of vitamin E were observed. The laboratory investigations were performed only at the start, and after 3 months and 6 months of vitamin E therapy.

Data were provided as mean $\pm$ SD. Differences between controls and the patient group were analyzed using chi-square and analysis of variance. The two-tail test for significance of before and after vitamin E treatment and 95% confidence limits were used to evaluate the difference.

Results

The clinical and biochemical data are summarized in Table 1. Twenty-eight patients who enrolled in this study expressed high oxidative stress compared with the control as shown in Table 2.

The levels of plasma malondialdehyde (MDA) and red blood cell glutathione peroxidase activity were significantly high in IgA patients. The glutathione (GSH) and red blood cell vitamin E were significantly low in the patient group. No change in catalase and superoxide dismutase (SOD) activities was observed.

Renal function study was done on all patients who revealed proteinuria of 0.86 $\pm$ 0.68 g/day. There were no significant differences in urine β_2–micro-globulin and creatinine clearance but urine N-acetyl glucosaminidase was increased significantly between IgA patients and controls as shown in Table 3.

Table 1. Clinical and biochemical data of controls and patients

Parameter	Controls	Patients (n=28)			
	(n=32)	0 Month	3 Months	6 Months	9 Months
Systolic Blood Pressure, mmHg	106.56 ± 10.45	127.0 ± 15.59*	121.74 ± 16.42*	119.44 ± 11.62*	120.0 ± 10.0
Diastolic Blood Pressure, mmHg	72.76 ± 19.62	79.0 ± 9.12	76.09 ± 8.34	72.78 ±5.74	72.86 ± 4.88
24 hr Urine Protein, g/D	0.29 ± 0.16	0.86 ± 0.7	0.873 ± 1.04	0.85 ±1.00	0.877 ± 0.253
Ccr, ml/min	86.66 ± 18.93	91.92 ± 31.33	94.11 ± 28.88	95.42 ± 26.25	88.88 ± 24.78
Serum Albumin, g/dl	4.92 ± 0.23	4.34 ± 0.419	4.68 ± 0.56	4.38 ± 0.36	4.36 ± 0.35
Serum Cholesterol, mg/dl	213.21 ± 33.95	204.2 ± 32.43	214.26 ± 33.06	207.89 ± 38.26	201.71 ± 29.70
Serum Triglyceride, mg/dl	97.93 ± 41.77	124.90 ± 91.88	123.87 ± 72.69	134.0 ± 86.70	117.57 ± 66.85

Values are mean ± SD, *p < 0.05 (control versus patient)

Table 2. Antioxidation enzymes and vitamin, lipid peroxidation product (malondialdehyde, MDA) in controls and patients

Parameter	Controls	Patients (n=28)			
	(n=32)	0 Month	3 Months	6 Months	9 Months
Erythrocyte:					
GSH-Px, U/gHb	27.48±7.86	38.52±15.53*	23.97±7.63**	25.22±9.72**	38.90±14.0*
Catalase, 10^4U/gHb	7.54±1.91	6.45±2.24	6.90±2.91	7.51±2.11	6.5±2.3
GSH, mg/dl	76.70±22.94	44.80±9.70*	32.45±6.74*	39.95±7.77*	45.0±9.8*
SOD, U/gHb	2038±647	2115±1228	1939±963	1935±464	2100±1100
Lipid peroxidation:					
P.MDA, mM	0.37±0.05	1.15±0.45*	0.86±0.30*.**	0.78±0.26*.**	1.1±0.3*
Antioxidant vitamin:					
RBC.Vitamin E, mM	7.84±1.04	5.07±2.42*	15.70±3.37*.**	12.90±3.58*.**	4.95±2.4*

Values are mean ± SD
* p < 0.05 (control versus patient)
** p < 0.05 (patient versus patient at 0 month)

Table 3. Urine protein, N-acetylglucosaminase (NAG), beta-2-microglobulin (B-2-M) in controls and patients

Parameter	Controls	Patients (n=28)			
	(n=32)	0 Month	3 Months	6 Months	9 Months
NAG µ/gCr	9.04 ± 4.02	13.23 ± 5.2*	12.29 ± 5.54*	13.63 ± 6.59*	13.6 ± 6.0*
B-2-M µg/gCr	65.5 ± 48.1	123.2 ± 146.0	164.8 ± 231.4	162.6 ± 234.7	160.0 ± 210.0
24 hr Urine Protein, g/D	0.29 ± 0.16	0.86 ± 0.7	0.873 ± 1.04	0.85 ±1.00	0.877 ± 0.253
Ccr, ml/min	86.66 ± 18.93	91.92 ± 31.33	94.11 ± 28.88	95.42 ± 26.25	88.88 ± 24.78

Values are mean ± SD
* p < 0.05 (control versus patient)

The effect of vitamin E therapy is also demonstrated in table 2 and table 3. The end product of lipid peroxidation as measured by plasma malondialdehyde (MDA) was significantly decreased after 3 and 6 months respectively of vitamin E supplementation ($p < 0.001$) as shown in table 2. Red blood cell vitamin E was increased to above normal levels as shown in table 2 (5.80 ± 2.98 VS 15.70 ± 3.37 μM, $p < 0.001$). However, the levels of antioxidant enzymes varied after vitamin E treatment. The activity of glutathione peroxidase (GSH-Px) and GSH decreased significantly after 3 and 6 months. The levels of superoxide dismutase activity had a trend of reduction but it was not statistically significant compared to the beginning of therapy. Catalase activity was also elevated but not statistically significantly.

There was no significant change in proteinuria, creatinine clearance, urine β_2-microglobulin and N-acetyl glucosaminidase enzymes both before and after vitamin E supplementation. After 3 months of cessation of vitamin E therapy, the patients had elevated plasma MDA and a reduction in red blood cell vitamin E as shown in Table 2.

Discussion

There is much evidence that reactive oxygen molecules contribute to organ injury in many systems, including the heart, liver, and central nervous system [28-31]. Oxygen free radicals have also been implicated in ischemia reperfusion renal failure and acute toxin-induced nephropathy[32-34]. Finally, initiation and progression of chronic glomerular and tubulointerstitial disease have been related to oxidant damage, and antioxidant treatment protects against progressive deterioration in several kidney diseases[35-39]. In an experimental model of IgA nephropathy, administration of vitamin E prevented hematuria, lowered proteinuria, stabilized renal blood flow, and reduced lipid peroxidation of the renal parenchyma[17].

An experimental model of IgA nephropathy was induced in male Lewis rats by oral immunization with 0.1% bovine γ-globulin (BGG) contained in their drinking water for 8 weeks. The BGG immunization regimen induced mesangial IgA deposition in all the rats. The protective effects of dietary vitamin E supplementation included less hematuria, reduced proteinuria, increased renal blood flow and less glomerular hypertrophy. A reduction in renal cortical malondialdehyde content and transforming growth factor β_1- gene expression were demonstrated. It concluded that dietary treatment with vitamin E attenuated renal functional and structural changes. These actions were associated with diminished oxidant damage to the renal parenchyma[40]. Protection against glomerular injury with a vitamin E – enriched diet has also been observed in chronic puromycin aminonucleoside nephropathy, a much more severe glomerulopathy[41]. The degree of preservation of GFR and renal plasma flow (RPF) achieved by vitamin E supplementation is comparable to the protection elicited by administration of a thromboxane synthesis inhibitor in experimental IgA nephropathy[42].

The association of increased renal lipid peroxidation and glomerular hypertrophy has been observed in other experimental kidney diseases such as chronic streptozocin-induced diabetes[43] and puromycin aminonucleoside nephropathy[41,44]. Oxidant stress may stimulate mesangial cell proliferation and extracellular matrix production, yielding glomerular hypertrophy. Reversal of glomerular enlargement by vitamin E occurred in the absence of increased kidney size. The protective effect of vitamin E in the face of improved GFR and RPF suggests that in the setting of this mild glomerulopathy, glomerular hypertrophy may be a more important factor in determining progressive loss of renal function[45,46].

IgA nephritis patients who had high oxidative stress, could compensate themselves by an increase in GSH-Px activity and a decrease in the level of GSH. Vitamin E also expressed low levels after amelioration of the oxidative stress. After vitamin E supplementation, the oxidative stress was improved, and GSH-Px activities were reduced until near normal but GSH was still high as well as MDA level. It demonstrated that the process of oxidative stress was not completely terminated. When vitamin E was withdrawn after 3 months, the level of RBC vitamin E was again decreased and GSH-Px activities were increased as at the beginning.

This preliminary report suggests that there is a reduction in oxidative stress after vitamin E supplementation. Although red blood cell vitamin E increased to the normal level the plasma MDA was still higher in IgA patients than in controls after 6 months of vitamin E supplementation. Antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase activities showed improvement but not in the normal range. Therefore, the oxidative stress process continued and could not be ameliorated completely.

Our findings indicate that administration of vitamin E can reduce oxidant stress. While vitamin E had no effect on the extent of mesangial IgA deposition, it is unlikely that antioxidant therapy altered the

immunologic basis of the disease; instead, it inhibited the subsequent inflammation in glomeruli. The patients in this study had a mild form of IgA nephropathy, manifested as hematuria, low-grade proteinuria, and normal creatinine clearance. Additional therapy is required to normalize oxidant stress such as concurrent exogenous administration of antioxidant enzymes, for example, superoxide dismutase (SOD) or catalase. Glucocorticoids have previously been demonstrated to affect the function of infiltrating cells by suppressing the generation of reactive oxygen metabolites produced during phagocytosis[47]. They can raise glomerular antioxidant enzyme activity both in vivo[48] and in vitro[49]. We concluded that increased oxidative stress is associated with patients with IgA nephropathy. Dietary treatment with an antioxidant agent such as vitamin E in addition to current medication might play an important role in the course of the IgA patients.

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ฤทธิ์ของ α-tocopherol ต่อภาวะออกซิเดทีฟ สเตรส และหน้าที่ไตในผู้ป่วยโรคไตชนิด IgA

ลีนา องอาจยุทธ, สมพงษ์ องอาจยุทธ, ไพศาล ปาริชาติกานนท์

ผู้ป่วย IgA nephropathy พบมากในประเทศไทย ซึ่งประมาณร้อยละ 25 ของผู้ป่วยเหล่านี้ จะกลายเป็นไตวายเรื้อรังระยะสุดท้ายในเวลา 5-25 ปี มีรายงานการเกิด ออกซิเดทีฟ สเตรส สูงในสัตว์ทดลองที่เป็น IgA nephritis ซึ่งทำลายเนื้อไตมากขึ้น รายงานนี้ได้ศึกษาผู้ป่วย idiopathic IgA nephropathy จำนวน 28 ราย เพื่อหาหลักฐานของออกซิเดทีฟ สเตรส ก่อนและหลังการให้วิตามิน อี ซึ่งเป็นสารแอนติออกซิแดนท์ ขนาด 400 มก.ต่อวัน เป็นเวลานาน 6 เดือน ผลการศึกษาพบว่า plasma MDA หรือ มาโลนไดอัลดีไฮด์ ซึ่งเป็นผลลัพธ์ของ ออกซิเดทีฟ สเตรส สูงจริงในผู้ป่วยอย่างมีนัยสำคัญทางสถิติ และลดลงหลังให้วิตามิน อี (1.15 ± 0.45 และ 0.86 ± 0.30 ไมโครโมล, p < 0.0001) วิตามิน อี ในเม็ดเลือดแดงสูงขึ้น (5.07 ± 2.42 และ 15.70 ± 3.37 ไมโครโมล, p < 0.001) สารแอนติออกซิแดนท์เอนไซม์ เช่น กลูตาไทโอน เพอรออกซิเดรส มี activity ลดลง ส่วน คาตาเลส และ ซูเปอร์ออกไซด์ ดิสมิวเทส ไม่เปลี่ยนแปลง กลูตาไธโอน มีค่าลดลง ส่วนหน้าที่ไต ได้แก่ creatinine clearance, โปรตีนในปัสสาวะ, β_2-m และ NAG ในปัสสาวะไม่มีการเปลี่ยนแปลง จากการศึกษานี้ สนับสนุนว่า ผู้ป่วย IgA nephropathy ที่มี ออกซิเดทีฟ สเตรส สูง และวิตามิน อี ต่ำ การให้วิตามิน อี สามารถลดภาวะดังกล่าวได้ ควรศึกษาการให้ แอนติออกซิแดนท์ ระยะยาวต่อไปว่าจะสามารถช่วยให้หน้าที่ไตดีขึ้นจริงหรือไม่