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Vitamin E treatment of focal segmental glomerulosclerosis: results of an open-label study

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Abstract Experimental data indicate that excessive production of reactive oxygen molecules contributes to progressive renal injury and that treatment with antioxidants attenuates this damage. Therefore, we investigated whether vitamin E supplementation could ameliorate renal disease and reduce proteinuria in children with a variety of kidney disorders. Vitamin E, 200 IU twice daily, was administered orally to 11 children with focal segmental glomerulosclerosis (FSGS) (group A) and 9 patients with miscellaneous kidney diseases (group B) [Henoch-Schönlein purpura nephritis (*n*=3), urinary tract anomalies (*n*=2), non-specific immune complex glomerulonephritis (*n*=2), IgA nephropathy (*n*=1), and reflux nephropathy (n=1)]. The duration of vitamin E treatment, when no other therapy was introduced, was 2.9±0.4 months. Proteinuria was determined by measuring the protein:creatinine ratio (mg/mg) in an early morning urine specimen. In children with FSGS, administration of vitamin E lowered the protein:creatinine ratio in 10 of 11 patients from 9.7±5.1 to 4.1±1.1 ($P<0.005$). In contrast, among children with miscellaneous renal diseases, vitamin E had no beneficial impact on urinary protein excretion-protein:creatinine ratio 2.5±1.0 pre versus 2.4±1.2 post antioxidant. Vitamin E supplementation had no effect on glomerular filtration rate, serum albumin, or cholesterol concentration in either group of patients. These findings suggest that reactive oxygen molecules may play a more-prominent role in causing renal injury in patients with FSGS than in other kidney disorders. Antioxidant therapy may be a useful adjunct in the treatment of children with FSGS and proteinuria that is refractory to standard medical management.

Key words Focal segmental glomerulosclerosis · Antioxidants · Vitamin E · Proteinuria

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Introduction

Vitamin E was discovered by Evans and Bishop in 1922 and was isolated from wheat germ oil in 1936 [1]. Vitamin E is a naturally occurring lipid-soluble, chain-breaking antioxidant [2]. The most-important dietary sources of vitamin E are vegetable oils such as soybean, cottonseed, safflower, sunflower, and wheat germ oils [3]. The daily requirement for vitamin E in children is age-dependent and ranges from 2 to 7 IU (3–10 mg) daily [3].

There is increasing evidence that vitamin E has a beneficial effect on free radical-mediated diseases, including progressive renal injury [4, 5]. In animal models of IgA nephropathy and focal segmental glomerulosclerosis (FSGS), in which excessive production of oxygen free radicals is implicated in the pathogenesis of disease, dietary supplementation with vitamin E protects against renal dysfunction and structural damage to the kidney [6, 7].

Therefore, based on these experimental findings, we conducted a prospective open-label, non-placebo-controlled trial to test the hypothesis that the oral administration of vitamin E will reduce proteinuria in patients with renal disease that is refractory to standard medical therapy.

Patients and methods

Patients

The study included two patient groups. Group A was comprised of 11 subjects with biopsy-proven FSGS. Group B contained 9 patients with miscellaneous renal diseases. The diagnosis in these patients was: Henoch-Schönlein purpura (HSP) nephritis, *n*=3;

non-specific immune complex nephropathy, *n*=2; urinary tract anomalies, *n*=2; IgA nephropathy, *n*=1; and reflux nephropathy, *n*=1.

Vitamin E treatment

Patients were given vitamin E, 200 IU twice daily, by mouth. Vitamin E was purchased by the patient without a prescription, and no standard formulation was administered. Informed consent was obtained in each case prior to commencing vitamin E treatment.

Clinical definitions

The duration of vitamin E treatment was defined as the period of time, in months, during which no other therapy was introduced and the estimated glomrular filtration rate (GFR) remained within 25% of baseline. In particular, no immunosuppressive medications or angiotensin converting enzyme inhibitors (ACEI) were started during this period.

Analytical methods

Proteinuria was determined by measuring the protein:creatinine ratio (mg/mg) in an early morning urine specimen. The normal value is less than 0.2. This measurement was performed at the start and at the end of the vitamin E treatment period. The estimated GFR (ml/min per 1.73 m^2) was calculated using the appropriate length-serum creatinine formula [8, 9].

Statistical methods

Data are provided as mean (SEM). Differences between the two groups were analyzed with the Mann-Whitney test and were considered significant if the *P* value was <0.05.

Results

The clinical features of the two patient groups are summarized in Table 1. The age, sex distribution of the patients, duration of disease (in years) prior to initiation of vitamin E treatment, and duration of antioxidant therapy (in months) were comparable in groups A and B. Interestingly, 4 African-American children were included in group A but none in group B.

More patients with FSGS than with miscellaneous renal diseases had been treated with immunosuppressive medications prior to starting vitamin E therapy. Among the children in group A, corticosteroid therapy was uniformly ineffective in 8 patients treated with this medication, and the other immunosuppressive agents did not induce a sustained reduction in proteinuria. In group B, treatment with oral corticosteroids was associated with a decrease in urinary protein excretion in the 3 patients with HSP nephritis, but there was no beneficial effect in 1child with non-specific immune complex nephropathy. A similar number of children in the two groups had received antihypertensive drugs, including ACEI.

The period of vitamin E treatment was limited in most cases because alternative immunosuppressive medications or ACEI were subsequently introduced in an attempt to further reduce urinary protein excretion. In group A, 5 patients were taking other drugs (3 were taking more than one medication) during the vitamin E treatment period. Two children received furosemide, 2 were taking lovastatin, and 1 patient each was given prednisone, methylphenidate, nifedipine, and calcium carbonate. Among patients with miscellaneous renal diseases (group B), 1 patient was taking prednisone and another was receiving calcitriol. The corticosteroid dosage was unchanged in both patients receiving this drug concomitantly with vitamin E. There is no evidence that vitamin E exerts a beneficial impact on the therapeutic efficacy of the various medications that were prescribed during the vitamin E treatment period.

None of the patients reported any side effects related to the administration of vitamin E. Antioxidant therapy had no significant effect on the serum albumin and cholesterol concentrations in patients from either group (Table 2). The estimated GFR remained within 25% of the baseline value during the period of vitamin E therapy in patients with FSGS and in those with miscellaneous renal diseases (Table 2). There was no correlation between the alteration in GFR and the change in urinary protein excretion observed in patient group A or B.

Table 1 Clinical features of the patients with focal segmental glomerulosclerosis (group A) and those with other renal diseases (group B) (*W* white, *B* black, *H* Hispanic, *ACEI* angiotensin converting enzyme inhibitor)

	Group A (*n*=11)	Group B (*n*=9)
Age (years)	12.9±1.2	13.2±1.8
Sex (M:F)	6:5	7:2
Ethnicity (W:B:H)	6:4:1	7:0:2
Duration of disease prior to vitamin E (years)	2.0±0.8	1.4±0.5
Duration vitamin E (months)	2.4±0.5	3.6±0.7
Prior treatment		
Prednisone	8	4
Cyclophosphamide	4	0
Cyclosporine	4	0
Antihypertensives (ACEI)	11 (8)	7 (7)

Table 2 Laboratory results of the two groups of patients before and after vitamin E treatment (*GFR* glomerular filtration rate)

	Group A (*n*=11)	Group B (*n*=9)
GFR (ml/min per 1.73 m^2)		
Pre	115±17	95±17
Post	104±14	102±21
Serum cholesterol (mg/dl)		
Pre	273±41	228±53
Post	251±45	188±9
Serum albumin (g/dl)		
Pre	3.3±0.3	3.5±0.2
Post	3.1±0.3	3.6±0.2

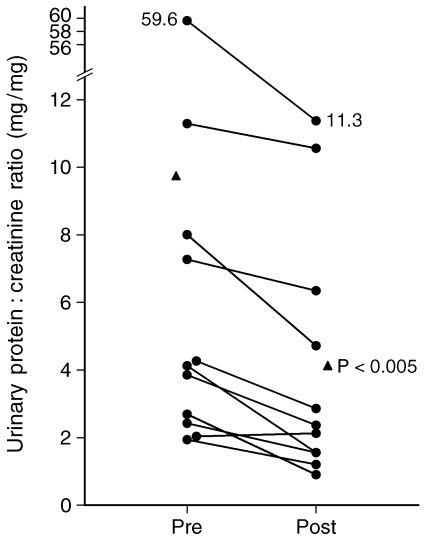

Fig. 1 Urinary protein excretion [protein:creatinine ratio (mg/mg) in an early morning specimen] in the patients with focal segmental glomerulosclerosis (group A, *n*=11). The lines connect the values prior to and at the completion of vitamin E treatment. The mean values are indicated by the *triangles*

However, vitamin E supplementation had a markedly different effect on urinary protein excretion in the two patient groups. In the children with FSGS (group A), 10 of 11 patients showed a decrease in proteinuria (Fig. 1). The urinary protein:creatinine ratio declined from 9.7±5.1 at the start of vitamin E supplementation to 4.1±1.1 at the completion of the vitamin E treatment period, a 58% reduction ($P<0.005$). This change was still significant if the patient with the highest urinary protein excretion was excluded from the analysis. There was a significant relationship between the initial amount of proteinuria and the degree of reduction in urinary protein excretion that was achieved following vitamin E treatment ($P<0.01$). However, the magnitude of the reduction in proteinuria was not related to the percentage of sclerotic glomeruli or the degree of tubulointerstitial changes in the renal biopsy specimens obtained from the patients with FSGS.

In contrast, in the patients with miscellaneous renal diseases (group B), while proteinuria was decreased in 6 of the 9 subjects, the overall effect was much less marked than in group A. Thus, the urine protein:creatinine ratio was virtually unchanged: 2.5±1.0 pre vitamin E versus 2.4±1.2 post vitamin E treatment ($P>0.7$). If patients in group B were further divided into two subgroups – those with anatomical abnormalities (n=3) and those with glomerular disease (n=6) – there was still no change in proteinuria in response to vitamin E treatment. Thus, in the children with primary urological disease, the urine protein:creatinine ratio was 2.4±0.9 pre vitamin E versus 2.1±0.7 post vitamin E treatment, while in children with glomerulopathies, the urine protein:creatinine ratio was 2.6±1.6 before starting vitamin E and 2.6±1.8 at the completion of the vitamin E treatment period.

Discussion

There is much evidence that reactive oxygen molecules contribute to organ injury in many systems, including the heart, liver, and central nervous system [10–13]. Oxygen free radicals have also been implicated in ischemia-reperfusion renal failure and acute toxin-induced nephropathy [14–16]. Finally, initiation and progression of chronic glomerular and tubulointerstitial disease have been related to oxidant damage, and antioxidant treatment protects against progressive deterioration in kidney disease [17–21]. 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 [6]. In a rat model of FSGS induced by serial injections of puromycin aminonucleoside, protective effects of dietary vitamin E supplementation included decreased urinary protein and albumin excretion, reduced hypoalbuminemia and hyperlipidemia, stabilization of the GFR, improved tubular function, diminished glomerulosclerosis and tubular interstitial fibrosis, and reduced renal and glomerular hypertrophy. These actions were associated with diminished oxidant damage to the renal parenchyma [7].

This preliminary report suggests that there is a beneficial effect of antioxidant therapy in the clinical management of pediatric patients with FSGS who have persistent proteinuria that is refractory to standard medical therapy. Proteinuria is a hallmark of glomerular disease and reduction in urinary protein excretion is often used as a surrogate marker for diminished glomerular barrier dysfunction [22]. The degree of reduction in urinary protein excretion that can be achieved with vitamin E therapy may not be of sufficient magnitude to favorably impact on edema and other complications of the nephrotic syndrome. Nonetheless, if proteinuria per se is injurious to the renal parenchyma [23–25], then any decrease in proteinuria may be associated with a parallel reduction in the rate of progression of glomerular disease [26]. The estimated GFR did not change appreciably during the vitamin E treatment period. There may have been subtle changes in GFR that were not detected using the serum creatinine-body length formulae. However, this makes it even less likely that the reduction in proteinuria was due to a significant decline in kidney function. Whether the vitamin E-induced decrease in proteinuria in children with FSGS is linked with long-term preservation of renal function must be determined in studies with a prolonged follow-up period which incorporate more-sensitive methods for measuring GFR.

Based on the disparate effect of vitamin E treatment in children with FSGS versus those with miscellaneous renal diseases, it would appear that oxygen-free radicals may contribute more prominently to progressive renal injury in FSGS than in the other kidney disorders studied. The observed benefit of vitamin E treatment within 1 month is consistent with a direct effect on immunoeffector cells that may mediate the increased glomerular

permeability to protein [27]. Alternatively, the antioxidant may act in a non-specific manner, e.g., reduction in transforming growth factor-β bioactivity and extracellular matrix protein gene expression, to diminish interstitial inflammation and fibrosis [28].

Additional studies are required to clarify the mechanism of action of vitamin E in reducing urinary protein excretion in children with renal disease. We acknowledge several shortcomings in our study. The protocol was open label and not a placebo-controlled trial. The dietary intake of our patients was not assessed, standardized, or controlled. While group A was a homogeneous sample of patients with FSGS, group B was heterogeneous and was comprised of several diseases. Thus, we cannot say with certainty that vitamin E is ineffective in diseases other than FSGS. Serum vitamin E levels were not measured to confirm compliance with the therapeutic regimen, and there was no direct confirmation that vitamin E exerts an anti-oxidant effect in our patient population. Finally, no attempt was made to systematically correlate the clinical response to vitamin E treatment and disease activity.

In summary, in this open-label study, we have demonstrated that short-term oral administration of vitamin E to children with FSGS leads to a nearly 60% reduction in the urinary protein:creatinine ratio. This effect is not observed in pediatric patients with other renal diseases. Further evaluation of the efficacy of antioxidant treatment is warranted, because it is a safe, well-tolerated dietary supplement that may be a useful adjunct in the clinical management of children with FSGS. In order to confirm the findings in this report, the Society for Pediatric Research is supporting a multi-center, double-blind, placebo-controlled trial of vitamin E as an antioxidant in the treatment of FSGS.

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