Nephroprotective effect of vitamin E added to angiotensin receptor blocker in patients with diabetic nephropathy

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ABSTRACT

Background: Diabetes mellitus is a condition associated with increased oxidative stress as a consequence of hyperglycemia. Therefore, the use of antioxidants in people with diabetes has been advocated. Vitamin E is the most prevalent naturally occurring anti-oxidant.

Aim: To evaluate the effect of the combination of angiotensin receptor blocker (ARB) and vitamin E on urine protein in patients with diabetic nephropathy.

Methods: One hundred and six patients with diabetic nephropathy, who visited the Alsader medical city in Najaf governorate and Al-Furat Al-Awsat general hospital in Kufa, were investigated, 39 of them are type 1diabetics, and 67 of them are type 2 diabetics. Each patient was followed up for 3 months with valsartan (160mg/day), then for 3 months with addition of tocopherol (400mg). At the screening visits, proteinuria was determined in two 24 h urine sample, arterial blood pressure was measured twice at ten minutes rest with 2 minutes interval and serum level of potassium, sodium & creatinine were determined.

Results: Proteinuria was significantly lowered when tocopherol 400mg was added to valsartan, as compared with valsartan without tocopherol. Valsartan alone caused a mean reduction of 24 h urine protein of 27% from the baseline, while the addition of tocopherol caused a mean reduction of 24 hour proteinuria of 30% from result of valsartan. That is mean the combination therapy of valsartan and tocopherol caused a reduction in proteinuria of 44% from baseline.

Conclusion: The current study suggests that combination therapy of ARB and vitamin E offers an additional antiproteinuric and nephroprotective effect.

Recommendation: Antioxidants, in particular vitamin E have promising nephroprotective effects. However, studies on other antioxidants like vitamin C are needed in the efforts of prevention of diabetic nephropathy

Introduction

Diabetic Nephropathy (DN) is one of the major cause of the end-stage renal diseases worldwide [1]. Despite the convincing evidence that antihypertensive treatment, particularly with ACE inhibitor and ARB interfere with renal disease progression [2], progression still cannot be completely halted and there is a desire need for additional therapeutic interventions [3].

Diabetes is a condition associated with increased oxidative stress as a consequence of hyperglycemia [4].Therefore, the use of antioxidants in people with diabetes has been advocated. Vitamin E is the most prevalent naturally occurring antioxidant and has been shown to retard atherosclerosis in animal model [5].

The antioxidative properties of vitamin E in human cells are well established [6].Vitamin E is a mixture of fat soluble tocopherol and tocotrienol, among which tocopherol has the highest biological activity [7].Vitamin E is the main lipophilic antioxidant in human [8]. Administration of vitamin E was reported to reduce oxidative damage in human red blood cells, platelets and peripheral mononuclear cells [9, 11]. The effect of administration of vitamin E were also investigated in various oxidative stress – related conditions, such as accelerated atherosclerosis[12], coronary heart diseases [13], and resistance to erythropoietin therapy [14]. In the current study, the effect of the combination of angiotensin receptors blockers and vitamin E on urine protein in patient with diabetic nephropathy was evaluated.

Methods

One hundred and six patients with diabetic nephropathy, who visited the Alsader medical city in Najaf governorate and Al-Furat Al-Awsat general hospital in Kufa were included in this study. Thirty nine of them were type 1 diabetics and 67 of them are type 2 diabetics. Diabetic nephropathy was diagnosed and patients were enrolled by using the following inclusion criteria: persistent proteinuria>300 mg/24 h in two out of three consecutive determinations, presence of diabetic retinopathy and no clinical or laboratory evidence of other kidney or renal tract diseases [15, 16]. Exclusion criteria at the start of the study were: serum potassium level> 4.8 moll/L, pregnancy, alcohol or medicine abuse, inability to understand patient information, systolic blood pressure <100 mm Hg and GFR< 30 ml/min.

One hundred and fifty patients were screened and 106 of them fulfilled the inclusion criteria, so they were included in present study. Each patient was followed up

for three months with valsartan (160mg/day), then for three months with the addition of tocopherol (400mg). At the screening visit, proteinuria was determined in two 24 h urine sample, arterial blood pressure was measured twice at ten min rest with two min interval, and serum potassium, sodium, creatinine, GFR were determined. At the end of treatment period we assessed clinical end points, including the primary end point proteinuria, and the secondary end points arterial blood pressure and GFR. All patients gave their informed consent to participate in the study.

At screening, normally distributed variables are expressed as mean ±SD, otherwise as median. During tocopherol treatment and other part of treatment, normally distributed values are expressed as mean ±SD. When evaluating the effect of vitamin E, comparisons of normally distributed parameters (albuminuria and serum creatinine) were done with a student t-test. P value<0.05 was considered significant (two –tailed).

Results

Characteristics at screening of 106 patients included in this study are shown in table 1.

Proteinuria was found to significantly lower when tocopherol 400 mg was added to valsartan, as compared with valsartan without tocopherol (Table 2). Valsartan alone caused a mean reduction of 24 h proteinuria of 27% from baseline, while the addition of tocopherol caused a mean reduction of 24 hour proteinuria of 30% from the result of valsartan (Table 2), that mean the combination therapy of valsartan and tocopherol caused a reduction of proteinuria of 44% from the baseline proteinuria. There was no any observed increase in serum potassium or serum creatinine or GFR (Table 2)

Table 1:

Baseline clinical data of 106 patients with diabetic nephropathy

Characters	Values
Age (year)	36±15
Sex (male/female)	55/51
Duration of diabetes (years)	11 ± 8
Arterial blood pressure (mmHg.)	131 ±12 / 70 ± 15
Proteinuria (gm. /24 hrs.)	1.5 ± 0.9
GFR(ml/min)	60 ± 24
Serum potassium(moll/l/L)	4.0±0.3

*p value is significant.

Table2:

Response to three months treatment with tocopherol 400mg./day in106

Parameters	Without tocopherol	With tocopherol	P-value
Proteinuria (gm./24 hrs.)	1.2 ± 0.62	0.84±0.8	<0.001*
Blood pressure (mm Hg)	125± 14/ 66 ± 12	124±16 / 66±12	NS
GFR (ml/min.)	61 ± 21	60±23	NS
Serum potassium (mmol/L)	4.0 ± 0.4	4.1±0.4	NS

Patients with DN receiving valsartan (160 mg/day).

cell

Discussion

The major finding in our study is that the combination therapy of tocopherol (400 mg/day) and ARB (Valsartan 160 mg/day) in patients with DN caused a mean reduction of 44% in 24 h urine protein, in comparison to 27% reduction in 24 h urine protein when valsartan used alone. This finding suggest that the supplementation of tocopherol provided an additional antiproteinuric effect.

Diabetes is a condition associated with increased oxidative stress as a consequence of hyperglycemia [2, 16]. Oxidative stress is related to an imbalance between production of reactive oxygen species and protective detoxifying mechanism during physiological and pathological conditions [17, 18]. The ant oxidative properties of vitamin E in human s are well established [9, 11]. In addition to its ant oxidative properties, vitamin E also reduces the cytotoxic effect of oxidized lipoprotein, smooth muscle cell proliferation, platelets adherence and aggregation, and inflammation, and it improves endothelial function [19, 20]. Moreover, observational studies have suggested that supplemental vitamin E users had lower rate of coronary events [19, 20]. Vitamin E was also proposed for prevention of micro vascular complications of diabetes [21]. It is the most important lipophilic anti-oxidant in human; it contribute to membrane stability and protects critical cell structures against harm form oxygen free radicals reactive lipoperoxides, which is relevant for several human pathological status, including kidney diseases.

In conclusion. Our study suggests that combined therapy of AR blocker and vitamin E offers additional anti proteinuric and nephroprotective effects, this effect may be not obtained by immunotherapy of vitamin E in some studies [4]. Combination therapy should be considered in diabetic renal diseases especially if the disease is progressing with ARB treatment alone. Antioxidants, in particular vitamin E have promising nephroprotective effects. However, studies on other antioxidants like vitamin C are needed in the efforts of prevention of diabetic nephropathy.

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