Abstract
Proteinuria and hypertension are predictors of poor renal and cardiovascular outcome in patients with diabetes [1,2]. Antihypertensive treatment especially with ACE inhibitors (ACEI) has been shown to reduce albuminuria, to diminish loss of kidney function and to improve survival in type 1 diabetic patients with diabetic nephropathy (DN) [1-4].

Introduction
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Dual Blockade of Renin – Angiotensin System in Patients with Diabetic Nephropathy
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At the Steno Diabetes Center ~30% of type 1 patients with DN have albuminuria >135 and/or >85 mmHg despite antihypertensive combination doses of ACEI and diuretic [5]. Recently a superior effect of dual blockade of renin-angiotensin-system (RAS) compared with single blockade has been reported in diabetic patients with microalbuminuria[6,7]. Therefore we evaluated the short term effect of dual blockade of the RAS by adding valsartan and angiotensin II receptor blocker (ARB) in patient with DN on conventional antihypertensive treatment including recommended doses of captopril.

**Subject and Methods**

From Al-Hakeem hospital and Al- Furat A-Awsat hospital we included 12 patients with DN, 7 of them are type 1 DM, and 5 are type 2 DM on conventional antihypertensive treatment, as defined below.

DN was diagnosed if following criteria were fulfilled: persistent proteinuria >300mg/24 hr in two out of three consecutive determinations, presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract diseases [8,9]. Diabetic nephropathy responding insufficiently to conventional antihypertensive treatment with the recommended doses of captopril 100 mg/day.

All patients with type 2 DM are on oral hypoglycemic agent (glibenclamide 5-10 mg/day, and all patients with type 1 DM are dependent on insulin treatment received at least two daily injection of insulin.

Exclusion criteria at the start of the study were: serum potassium >4.8mmol/l, pregnancy, no use of contraceptive, age <18 years, alcohol or medicine abuse, inability to understand the patient information, contraindication to treatment with ARAs, systolic blood pressure <100 mmHg, GFR<20 ml/min.

Fifteen patients were screened and 12 of them fulfilled all inclusion criteria, did not any exclusion criteria are were included in the study.

**Methods**

Each patient followed up for 2 months with conventional antihypertensive treatment, then for 2 months with addition of valsartan (180 mg). At the screening visit albuminuria was determined in two 24 hr urine sample, arterial blood pressure was measured twice at 10 min rest with 2 min interval, and serum potassium, sodium, creatinine was determined. Blood pressure, serum potassium, and serum creatinine were measured 2 weeks after the beginning of each treatment period for safety reasons.

At the end of each treatment period we assessed clinical end points, including the primary end point albuminuria, and the secondary end points arterial blood pressure and GFR.

Drugs compliance was assessed by tablet count. All patients gave their informed consent to participate in the study.

**Statistics**

At screening, normally distributed variables are expressed as mean (SD), otherwise as median (range). During valsartan treatment and other part of treatment, normally distributed values are expressed mean (SE). When evaluating the effect of valsartan, all comparisons of normally distributed parameters (albuminuria, serum creatinine, and renin concentration) were done with a paired student t-test.

A linear regression analysis was made between the change in arterial blood pressure and the change in albuminuria. P-value <0.05 was considered significant (two-tailed).

**Results**

Characteristic at screening of 12 patients included in this study are shown in table (I).

The median duration of each treatment period was 62 days. Albuminuria, and
arterial blood pressure were significantly lower during dual blockade of the RAS when valsartan 160 mg was added to conventional antihypertensive treatment as compared with antihypertensive without valsartan table (II).

The addition of valsartan caused a mean reduction in 24 hr proteinuria of 40% (table (II)), we found a decline in systolic blood pressure of 9 mmHg, and a decline in diastolic blood pressure of 7 mm Hg.

**Table I** baseline clinical data in 12 patients with diabetic nephropathy (DN)

<table>
<thead>
<tr>
<th>Characters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
</tr>
<tr>
<td>Age (year)</td>
<td>41 ± 15</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/4</td>
</tr>
<tr>
<td>Duration of diabetes (year)</td>
<td>15 + 7</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td>144 ± 15 / 82 +10</td>
</tr>
<tr>
<td>Albuminuria (g/24 hr)</td>
<td>(1.2-2.3)</td>
</tr>
</tbody>
</table>

**Table II** Response to 2 months treatment with valsartan 160 mg /day in 12 patients with DN receiving captopril.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Without valsartan</th>
<th>With valsartan</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1.82(1.2-2.3)</td>
<td>0.98 (0.69-1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>146+4 / 80+2</td>
<td>138+4 / 75+5</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>51</td>
<td>53</td>
<td>NS</td>
</tr>
<tr>
<td>S.Cr (mmol/l)</td>
<td>141</td>
<td>143</td>
<td>NS</td>
</tr>
<tr>
<td>S.K (mmol/l)</td>
<td>4.3</td>
<td>4.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

GFR= glomerular filtration rate  
S.Cr= serum creatinine  
S.K= serum potassium

**Discussion**

The major finding in our study are that dual blocked of the renin-angiotensin system by the addition of valsartan 160 mg caused a reduction in patients with DN, this finding is in agree with the previous study [6,7].

The rational for dual blockade of the RAS is based on different mechanism of action of the two drug class [10]. Insufficient response to ACEI might be explained by incomplete blockade of the ACE enzyme or by generation of the angiotensin II by ACE-independent pathway such as chymase pathway [11]. The incomplete blockade possibly explains the observation that plasma angiotensin II levels return to normal after chronic ACEI use, a phenomena called ACE escape [12]. Therefor treatment with both ACEI and ARB may offer synergistic blocked of the RAS obtained with either drug group alone.

that the maximal antiproteinuric and antihypertensive effect of angiotensin II receptor blockade is present after <one month of treatment.

The correlation between change in blood pressure and change in proteinuria observed in our study has been demonstrated in several other studies as reviewed by Parving [15].

**Conclusion**

In conclusion, our study suggests that dual blocked of the RAS offers, additional renal and cardiovascular protection in patients with DN.

The long-term renoprotective effect of RAS blockade displays a marked between-patient heterogeneity, which is closely linked to between-patient differences in the intermediate parameters of blood pressure, proteinuria and renal haemodynamics, so the response-based treatment schedules, rather than fixed treatment schedules, may provide a fruitful strategy for more effective renoprotection [16]. Combination treatment should be considered in non-diabetic renal disease especially if the disease is progressing with ACEI treatment alone [17].

Ideally antihypertensive therapy should maintain or improve the patients quality of life without creating side effect or adverse laboratory effects. Among the available nine classes of antihypertensive drugs, ACEI and the ARB come close to meeting the description of an ideal drug. ARB and ACEI should be among the preferred first-step drugs for the treatment of hypertension [18].

**Reference**

9- Magensen C E ,Chachati A , Christensen C K et al ,Uremia Inverst 1985, 9,85.