Turkish Journal of Endocrinology and Metabolism, (2001) 1 : 25-29 **ORIGINAL ARTICLE**

# Effect of Angiotensin II Receptor Antagonist-Losartan on Adrenal Steroidogenesis and Glucose Metabolism in Diabetic Hypertensive Patients

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**In this study we aimed to examine the effect of losartan, the prototype of type 1 angiotensin II receptor antagonist, on adrenal steroidogenesis and glucose metabolism in diabetic patients. Ten female patients with Type 2 diabetes mellitus, aged 60.5±8.4 years (range 51-73 years) were studied. The study consisted of an 8-week 50 mg/day losartan therapy. Before treatment and in at two-weekly intervals clinic visits heart rate and blood pressure measurements were taken and serum glucose, fructosamine, urea, creatinine, sodium, potassium, uric acid, AST, ALT, total and HDL cholesterol, triglyceride, ACTH, DHEA-S $O_4$, androstenedione, 17-OH progesterone , aldosterone, and plasma renin activity levels were assayed. Basal and synacthen-stimulated adrenal steroidogenesis were evaluated before and at the 8 $^{th}$ week of losartan treatment. Losartan produced a significant decrease in both systolic and diastolic blood pressures. There was no statistically significant difference between biochemical results before and after the therapy. Serum cortisol levels after ACTH stimulation displayed an almost equal elevation in pre and post-treatment periods. We conclude that the angiotensin II receptor blocker, losartan, at a dosage of 50 mg once daily was significantly effective in decreasing both systolic and diastolic blood pressure and can be used safely in diabetic patients. We also demonstrated that losartan does not have any detrimental effect on adrenal steroidogenesis.**

**Key words: Losartan, Steroidogenesis, Type 2 Diabetes Mellitus, Hypertension**

## Introduction

Angiotensin II exerts its biologic effects through stimulation of specific membrane receptors that are located in various target organ tissues (1, 2). Losartan is the prototype of orally active type 1 angiotensin receptor ($AT_1$) antagonists which blocks the pressor and functional responses to angiotensin II (3-6). In clinical trials losartan was found to be an antihypertensive agent as potent as angiotensin converting enzyme inhibitors (8-10). It is proposed that angiotensin II receptor antagonists offer the advantages of increased selectivity and specificity without the adverse reactions associated with ACE inhibition (11-14). However, it is unclear what risks may be associated with sustained AII stimulation of AT-II receptors.

Losartan and other angiotensin receptor antagonists are phenyl tetrazole substituted imidazoles (3, 15, 16). Many other imidazole derivatives are shown to inhibit adrenal steroidogenesis. Ketaconazole, etomidate and micanazole are known imidazole derivatives which were shown to have inhibitory effects on the secretion of cortisol (17-19). In this study we aimed to examine the effect of losartan on adrenal steroidogenesis. We also evaluated the safety of losartan on lipid and glucose metabolism in Type 2 diabetic hypertensive patients.

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## Subjects and Methods

Ten female patients with Type 2 diabetes mellitus, aged 60.5±8.4 years (51-73 years) were studied. Patients with diastolic blood pressure between 90-115 mmHg were included in the study. All of them had been hypertensive for 7.6±2.4 years (3-10 years), but had not beeen taking medications for more than at least 4 weeks. They had been diabetic for 8.7±2.9 years (5-15 years). Patients with any evidence of renal or hepatic disease or concomitant use of any agent except sulphonylurea were not included in the study.

The study consisted of 8 weeks of 50 mg/day angiotensin II receptor antagonist-losartan therapy. In 2-weekly interval visits, heart rate per minute and blood pressure measurements were taken two times after at least 15 minutes of rest and after standing up for 3 minutes. Fasting blood glucose, fructosamine, urea, creatinine, sodium, potassium, uric acid, AST, ALT, total cholesterol, and triglyceride were assayed at every clinic visit. Hormonal evaluation comprised measurement of serum ACTH, DHEA-$SO_4$, androstenedione, 17-OH progesterone, aldosterone, cortisol and plasma renin activity before and after losartan therapy. Microalbuminuria was also investigated before and after the losartan therapy.

Stimulated adrenal steroidogenesis was performed before and after the treatment. Cortisol stimulation was induced by i.m. injection of 0.25 mg synthetic ACTH- synacthen (Ciba-Geigy, Basel, Switzerland), and blood samples were obtained at $30^{th}$, $60^{th}$, $90^{th}$ and $120^{th}$ minutes to measure serum cortisol levels.

Serum glucose, urea, creatinine, sodium, potassium, AST and ALT levels were measured with an auto analyser. Total cholesterol and triglyceride levels were measured using enzymatic methods. Urinary albumin excretion was assayed in 24 hour urine specimen by the RIA method. Fructosamine was measured by quantitative colorimetric determination (Sigma Diagnostics, St. Louis). Serum cortisol, DHEA-$SO_4$, androstenedione, 17-OH progesterone renin and aldosterone levels were assayed with commercially available RIA kits.

Results were analyzed by Student's t test for paired data. Analyses were performed with procedures in the Statistical Package for Social Sciences (SPSS). All tests of significance were two-tailed, and p values of 0.05 or less were considered statistically significant. Data was expressed as the mean ± SD.

## Results

Figure 1 displays mean systolic and diastolic blood pressure decrease during losartan treatment. Decreases in both systolic and diastolic blood pressures are significantly different even at the second week of losartan therapy. Heart rate, systolic and diastolic blood pressure in resting and upright position during the treatment period are shown in Table 1. Changes in systolic and diastolic blood pressures and heart rates after upright position did not show any significant difference throughout the treatment period.

There was no statistically significant difference between serum concentrations of glucose, fructosamine, potassium, total cholesterol, triglyceride, AST, ALT, urea and uric acid before and after 8 weeks of losartan therapy (Table 2). Plasma renin activity showed a significant increase only at $2^{nd}$ and $4^{th}$ weeks, where aldosteron level decrease was not significant. Although urinary albumin ex

**Table 1** . Systolic and diastolic blood pressures and heart rates with upright position by weeks of losartan treatment.

| | Systolic Blood Pressure mmHg | | Diastolic Blood Pressure mmHg | | Heart Rate | |
|---|---|---|---|---|---|---|
| | Resting | Upright | Resting | Upright | Resting | Upright |
| Baseline | 161 ± 16 | 159 ± 16 | 100 ± 7.1 | 95 ± 5.4 | 87 ± 9 | 92 ± 11 |
| $2^{nd}$ Week | 154 ± 7 | 149 ± 15 | 92 ± 7.4 | 89 ± 9.4 | 84 ± 7 | 89 ± 8 |
| $4^{th}$ Week | 148 ± 15 | 145 ± 13 | 88 ± 10.4 | 87 ± 11 | 81 ± 8 | 86 ± 8 |
| $6^{th}$ Week | 149 ± 18 | 145 ± 19 | 87 ± 11.1 | 86 ± 8.6 | 83 ± 9 | 88 ± 8 |
| $8^{th}$ Week | 147 ± 15 | 146 ± 14 | 88 ± 6.7 | 86 ± 6.9 | 82 ± 9 | 87 ± 8 |

**Table 2** . Serum glucose, fructosamine, potassium, total cholesterol, triglyceride, AST, ALT, urea, uric acid, renin activity, aldosterone levels and urinary albumin excretion by weeks of losartan treatment (* $p < 0.05$ vs baseline).

| | Baseline | 2nd Week | 4th Week | 6th Week | 8th Week |
|---|---|---|---|---|---|
| Glucose (mg/dl) | 180 ± 44 | 178 ± 54 | 178 ± 80 | 173 ± 51 | 164 ± 37 |
| Fructosamine (mg/dl) | 2.58 ± 0.23 | 2.41 ± 0.36 | 2.40 ± 0.57 | 2.46 ± 0.48 | 2.33 ± 0.55 |
| Potassium (mEq/L) | 4.2 ± 0.3 | 4.1 ± 0.3 | 4.2 ± 0.5 | 4.1 ± 0.5 | 4.1 ± 0.2 |
| T Cholesterol (mg/dl) | 217 ± 36 | 215 ± 52 | 214 ± 45 | 218 ± 46 | 210 ± 44 |
| Triglyceride (mg/dl) | 184 ± 93 | 203 ± 94 | 196 ± 81 | 200 ± 76 | 181 ± 79 |
| AST (U/L) | 33.7 ± 9.3 | 32.4 ± 8.4 | 34.3 ± 5.6 | 31.2 ± 7.5 | 31.2 ± 6.0 |
| ALT (U/L) | 24.3 ± 9.7 | 23.7 ± 7.7 | 25.4 ± 7.8 | 25.9 ± 7.2 | 26.8 ± 9.6 |
| Urea (mg/dl) | 31 ± 10 | 34 ± 14 | 29 ± 5 | 28 ± 6 | 26 ± 6 |
| Uric Acid (mg/dl) | 4.45 ± 0.86 | 4.13 ± 1.07 | 4.31 ± 0.99 | 3.73 ± 0.42 | 3.39 ± 1.21 |
| Plasma Renin Act. | 2.80 ± 1.41 | 3.98 ± 3.26 * | 4.42 ± 2.02 * | 3.47 ± 1.71 | 2.95 ± 1.76 |
| Aldosterone (pg/ml) | 201 ± 106 | 203 ± 127 | 204 ± 132 | 222 ± 226 | 169 ± 49 |
| Albuminuria (mg/24h) | 25.1 ± 37.4 | _ | _ | _ | 21.5 ± 29.8 |

cretion rate diminished after losartan therapy, it was not significantly different from pretreatment values.

Surrenal hormones were evaluated before and at the 8th week of losartan therapy (Table 3). No substantial difference was found in adrenal hormone levels after losartan treatment. Also insulin and C-peptide levels did not show any statistical significance. A diagram of the serum cortisol level after 0.25 mg synthetic ACTH stimulation performed before and after the 8th week of losartan therapy is shown in Figure 2. Cortisol levels displayed almost equal elevation in both conditions.

**Figure 1** . Change in systolic and diastolic blood pressures during losartan treatment.

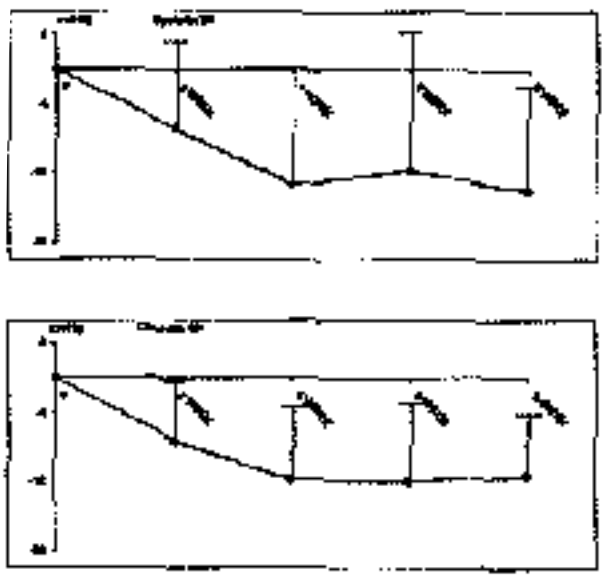
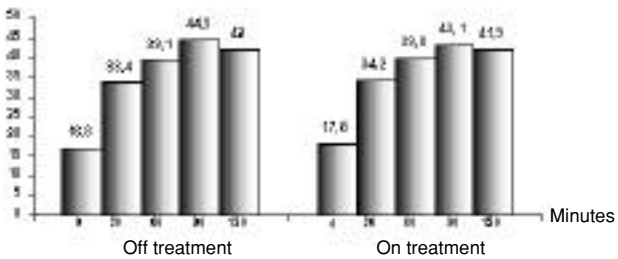


**Table 3**. Serum cortisol, dihydroepiandrosterone sulphate, androstenedione, 17-OH progesterone, insulin and C-peptide level differences during losartan treatment (NS: not significant).

| | Before Therapy | After Therapy | p |
|---|---|---|---|
| Cortisol (ug/dl) | 16.8 ± 4.8 | 17.8 ± 6.7 | N.S. |
| DHEA-SO4 (ug/dl) | 1.46 ± 1.44 | 1.05 ± 0.85 | N.S. |
| Androstenedione (ng/ml) | 1.75 ± 1.23 | 1.51 ± 0.80 | N.S. |
| 17-OH Progesterone (ng/ml) | 1.10 ± 1.17 | 0.85 ± 0.81 | N.S. |
| Fasting Insulin (mIU/ml) | 12.21 ± 9.15 | 10.29 ± 7.19 | N.S. |
| Fasting C-Peptide (ng/ml) | 5.85 ± 5.96 | 3.66 ± 5.96 | N.S. |

**Figure 2** . Effect of 8 week Losartan treatment on ACTH stimulated plasma cortisol levels.




## Discussion

ACE inhibitors are usually the drug of choice in diabetic hypertensive patients because of their confirmed beneficial effects especially on the progression of diabetic nephropathy (20). However, cough and angioedema are the two important side effects of ACE inhibition which is not related to blockade of angiotensin II production (21). Losartan

is the first of a new class of orally active angiotensin II receptor antagonists. In patients with essential hypertension, losartan effectively reduces blood pressure (11, 22). Because of improved specificity and selectivity on inhibition of the renin-angiotensin system it is considered to be used with an improved safety profile compared with ACE inhibitors that inhibit renin angiotensin system non-selectively (9, 12, 13). In the literature, the most frequently reported clinical adverse experiences considered as losartan related were headache (4.2%), dizziness (2.4%) and asthenia/fatigue (2.0%). Increased ALT was the laboratory adverse event with the highest incidence (1.9%) and hyperkalemia was reported in 1.5% of patients receiving losartan (6-8, 14). Furthermore, it has been shown that the safety profile remained unchanged during longer periods of treatment with losartan (9, 14).

Using conventional blood pressure measurements, we found that 8 weeks of treatment with losartan at the dosage of 50 mg once daily was significantly effective in decreasing both systolic and diastolic blood pressure in moderately hypertensive Type 2 diabetes mellitus patients. (Figure 1). None of the patients discontinued the 8 weeks of losartan therapy and they did not report any clinical adverse effect. We did not observe edema or postural hypotension. Fasting blood glucose and fructosamine levels did not differ during the losartan treatment. Serum levels of total cholesterol, triglyceride, potassium, urea, AST, ALT were statistically not different from the pretreatment values. Any detrimental effect on lipids, glucose or any other metabolic parameters was not observed. Urinary albumin excretion was with in normal levels and reduced slightly but not significantly after the treatment. We also observed minimally decreased serum uric acid level. We conclude that the angiotensin receptor blocker-losartan can be used safely in diabetic patients, and may best be used as an alternative therapy to ACE inhibitors in patients who are intolerant of ACE inhibition.

Imidazole derivative drugs have been shown to diminish cortisol pruduction by inhibition of adrenal cytochrome p-450 enzymes (23-25). This adverse effect has been used for the treatment of hyper-cortisolism (17, 26). Especially ketaconazole remains the available drug for the treatment of Cushing's syndrome which cannot be treated definitively by surgery (19, 24). It was also shown that, these drugs affect corticosteroidogenesis by normal, hyperplastic and adenomatous adrenal cells (27).

After 8 weeks of 50 mg/day losartan therapy serum levels of cortisol, dehydroepiandrosterone-sulphate, androstenedione and 17-OH-progesterone levels were close to those before the therapy. We also demonstrated that angiotensin II receptor antagonist therapy with 2-N-butyl-4chloro-5-hydroxy-methyl-1-imidazole (losartan) did not interfere with ACTH stimulated adrenal steroidogenesis. These data strongly suggests that treatment with angiotensin receptor antagonist-losartan does not have a detrimental effect on steroidogenesis.

The effectiveness of imidazole derivatives on the steroidogenesis differed. Ketocanozole predominantly blocks 17,20 desmolase, where as etomidate has a strong inhibitory effect on 11 beta-hydroxylase but only a weak inhibition of 17,20 desmolase (18, 23, 28). Ketaconazole treatment in patients with Cushing's syndrome showed various remission rates and these rates had been found altered in different etiologic types of Cushing's syndrome (25, 26). Sasaki (29) et al. also concluded that the effect of 50 mg/day losartan on adrenal biosynthesis was negligible. In the present study, although losartan is an imidazole derivative, we did not observe any effect on adrenal corticosteroidogenesis. This outcome may be due to the chemical difference between losartan and the other imidazole derivatives, or may be due to the dosage of losartan used in the study.

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