Effects of Low Doses of Captopril or Losartan in Improving Glycemic Control by Oral Hypoglycemic Agents in Type 2 DM Patients

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الخلاصة

أثبتت الدراسات الحديثة وجود ترابط بين ظاهرة قصور أفرار الأنسولين أو عدم فاعليته في تنظيم مستوى الكولوكوز في الجسم وفعالية نظام الرنين-انجيوتينسين من خلال دوره في تنظيم جريان الدم في البنكرياس. تم تصميم هذه الدراسة لقياس تأثير جرع قليلة من مادتي كابوترين ولوسارتون كعلاج تكميلي لحالات ضعف السيطرة على مستوى السكر في الجسم بواسطة خفضات السكر الفموية (مثل الكلينكمايد) لوحدها. تم أجراء الدراسة على 75 مريضاً بالناقص الثاني من داء السكري غير المسيطر عليه بالعلاج بواسطة الكلينكمايد، وتم تقسيمهم عشوائياً إلى ثلاثة مجموعات: الأولي (25 مريضاً) تم علاجهم بجرعة تهديئة تحتوي على اللاكتوز فقط أضافة إلى كلينكمايد 10 ملغ/يوم لمدة أربعة شهور؛ المجموعة الثانية (25 مريضاً) تم علاجهم بجرعة مقدارها 12.5 ملغ/يوم من مادة كابوتيريل أضافة إلى الكلينكمايد؛ والمجموعة الثالثة (25 مريضاً) تم علاجهم بجرعة مقدارها 25 ملغ/يوم من مادة لوسارتون أضافة إلى الكلينكمايد ولمدة أربعة شهور. بعد صيام لمدة 12 ساعة، تم أخذ عينات من الدم من جميع المرضى قبل بدء العلاج وبعد أربعة شهر لقياس مستوى الكولوكوز في الدم ومستوى كلوزة خضاب الدم، الببتيد-سي، الببتيد-ألبراتين، وأنزيمات الكبد (AST, ALT, ALP, GGT) في الدم كما تم جمع عينات من الأدرار لتحديد مستوى الألبومين الدقيق كمعايير لمتابعة وتقييم تأثير العلاج.

أظهرت النتائج بأن استخدام جرع قليلة من مادة كابوتيريل أو لوسارتون مع الكلينكمايد أدى إلى انخفاض مستوى الكولوكوز وكلوزة خضاب الدم متزامناً مع زيادة في مستوى الببتيد-سي مقارنة مع المرضى الذين تم علاجهم بجرعة التهديئة، بالإضافة إلى تحسين صورة الشحم وخفض مستوى طرح الألبومين في الأدرار. من خلال هذه النتائج يمكن الاستنتاج بأن التدخل في نظام الرنين-انجيوتينسين يزيد من حساسية أنسجة الجسم لفعالية الأنسولين وكذلك تحسين ال)-- (( نتائج في زيادة أفراره مما يؤدي إلى تحسين مستوى السيطرة على مستوى الكولوكوز في الدم.
Abstract:
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Cross-talk between the renin-angiotensin system (RAS) and insulin signaling has been demonstrated. The rennin angiotensin system (RAS) may regulate pancreatic islet blood flow, oxygen tension, and islet (pro) insulin biosynthesis. The present study was designed to evaluate the effect of low doses captopril and losartan, as adjunct treatment in uncontrolled type 2 DM patients treated with oral hypoglycemic agents alone.

This double-blind placebo-controlled clinical trial was conducted on 75 patients with uncontrolled type 2 diabetes mellitus; they are randomized into three groups:

Group A: includes (25) patients treated with placebo formula containing lactose only in addition to glibenclamide (10 mg/kg) for 4 months; group B: includes (25) patients treated with 12.5 mg captopril given once daily at bed time, for 4 months; group C: includes (25) patients treated with 25 mg losartan given as a single daily dose at bed time for 4 months; all patients take the test drugs in addition to the routinely administered oral hypoglycemic drug (glibenclamide 10 mg/kg). After 12 hours fasting, blood samples were collected from all patients to measure fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), C-peptide, triglyceride (TG), total cholesterol, low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), serum urea and creatinine, alanine transaminase, aspartate transaminase, alkaline phosphatase (ALP) and gamma glutamine transferees (GGT), and urine samples were obtained for assessment of microalbuminuria (MAU), before starting drug treatment (as zero time sample) and then after 4 months of treatment to follow the changes in the studied parameters.

Adjuvant use of low doses of captopril or losartan with the currently used oral hypoglycemic agents (glibenclamide) results in significant reduction in FPG and HbA1c levels associated with increase in C-peptide level compared to those treated with the oral hypoglycemic agents and placebo; additionally, lipid profile, MAU, renal and liver functions were significantly improved after 4 months of treatment.

Inhibition of RAS by ACEIs or AT1 antagonists (ARBs) increases insulin sensitivity and improves insulin secretion, where treatment of poorly controlled type 2 DM patients with captopril or losartan resulted in improving the response of target tissues to glibenclamide.

Key words: Captopril, Losartan, Glycemic control, Type 2 DM

Introduction:
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. The chronic hyperglycemia of diabetes is associated with long-term
damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [2].

Drug therapy for type 2 diabetes aims to control blood sugar levels both in the basal (fasting) state and postprandially; rational combinations of agents with different mechanisms of action can be used [3]. Although there are many strategies available for treating diabetes, but virtually all center on mitigating acute and chronic hyperglycemia and avoiding acute hypoglycemia [4], tightly controlling any hypertension, often with use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, as these have the additional benefit of being nephroprotective and increasing peripheral insulin sensitivity [5].

The rennin angiotensin system RAS may regulate pancreatic islet blood flow, oxygen tension, and islet (pro) insulin biosynthesis [6]. It might also mediate the generation of reactive oxygen species, thereby causing oxidative stress-induced pancreatic beta-cell apoptosis and fibrosis [7,8]. Moreover, findings that RAS blockade improved beta-cell secretory function and cell mass in experimental animal models of type 2 diabetes indicate that inhibition of RAS activation may play a pivotal role in protecting islet cell function, and furthermore may prevent the development of overt type 2 DM [9,10]. Such data supporting the involvement of the local pancreatic RAS in islet function, as well as a causal relationship between RAS activation and type 2 DM, and RAS induced beta-cell dysfunction, mandate further investigation into the role of RAS in the pathogenesis of the progressive islet impairment observed in patients with type 2 DM [11]. Large clinical trials have shown that inhibition of the renin-angiotensin system (RAS) can delay and/or prevent the onset of type 2 diabetes mellitus in high-risk individuals, such as those with hypertension or chronic heart failure, thus supporting the involvement of the local pancreatic RAS in islet function [12].

The present study was designed to evaluate the effect of low doses captopril and losartan, as adjunct treatment in uncontrolled type 2 DM patients treated with oral hypoglycemic agent (glibenclamide) alone.

Materialss and Methods:

Double blinded, placebo-controlled clinical study was conducted on 75 uncontrolled type 2 diabetic patients during the period from February 2007 to January 2008 at the National Diabetes Center, AL-Mustansriya University in Baghdad (35 male and 40 female) with age range (35-64 years), and with mean duration of diabetes of 5 years. All the selected patients have no other prominent pathological disorders like hypertension and IHD, and were already treated with the ordinary hypoglycemic agent glibenclamide, but with poor glycemic control as evidenced by abnormal values of fasting plasma glucose and glycated hemoglobin. The study protocol was approved by the committee for clinical research ethics in the University of Baghdad and ministry of Health, and all patients signed written consent before enrollment in the study, which is...
performed according to the following exclusion criteria: They should not have other prominent associated chronic disease like liver and kidney disorder and cardiovascular complications; patients who are pregnant and breast feeding are excluded. They should not be on insulin therapy or maintained on any type of antioxidant drugs, aspirin, and antihypertensive drugs.

The patients were randomized into three groups: Group A; include 25 patients treated with placebo formula containing lactose only for 4 months, in addition to the routinely used oral hypoglycemic agent (glibenclamide 10 mg/day) (SDI, Iraq); group B, include 25 patients treated with 12.5 mg captopril tablets (Medoche Ltd, Cyprus), given once daily at bed time for 4 months, in addition to the routinely used oral hypoglycemic agent (glibenclamide 10 mg/day); group C, include 25 patients treated with 25 mg losartan tablets (Asia, Syria), given as a single dose at bed time for 4 months, in addition to the routinely used oral hypoglycemic agent.

All patients were evaluated clinically and biochemically before starting the study and after 4 months, evaluation and follow up procedures include measurement of blood pressure, fasting plasma glucose (FPG) \cite{13}, glycated hemoglobin (HbA$_1c$) \cite{14}, triglyceride (TG) \cite{15}, cholesterol \cite{16}, low density lipoprotein (LDL-c), high density lipoprotein (HDL-c) \cite{17}, blood urea \cite{18}, serum creatinine \cite{19}, C-peptide \cite{20}, alanine transaminase, aspartat transaminase \cite{21}, alkaline phosphates (ALP) \cite{22}, gamma glutamyl transferase (GGT) \cite{23}, and microalbuminuria (MAU) \cite{24}.

**Results:**

The data presented in table 1 showed that there is a small non-significant change in FPG after 4 months treatment with placebo (2.2%), while there is a significant reduction in FPG in patients treated with captopril or losartan for 4 months (30.9 % and 7.4 % respectively, $P<0.05$). There is no significant change in HbA$_1c$ after 4 months in group A, but HbA$_1c$ significantly decreased due to treatment with captpril or losartan (17% and 5% respectively, $P<0.05$) compared to pre-treatment. There is a small decrease in C-peptide levels (0.53-0.56 ng/ml) after 4 months treatment with placebo. Meanwhile, significant elevation in C-peptide levels (0.56-1.33 ng/ml, $P<0.05$) due to treatment with captopril. Also a significant increase in C-peptide levels (0.54 ng/ml-1.03 ng/ml, $P<0.05$) reported after using losartan compared to pre-treatment levels (table 1).

In table 2, treatment with 12.5 mg captopril or 25 mg losartan for 4 months results in significant decrease in serum total cholesterol levels (20.5% and 15.8 % respectively, $P<0.01$) compared to pre-treatment levels, while no significant changes were reported in group A after 4 months. Table 2 also showed that triglyserides levels were significantly decreased in patients treated with captpril or losartan with glibenclamide (26.5% and 11.5 % respectively, $P<0.001$) compared to pretreatment levels, while no significant difference reported in placebo-treated group after 4 months of treatment.
Concerning HDL-c levels, no significant changes reported in group A (placebo+glibenclamide), while adjunct use of captopril or losartan with glibenclamide significantly increases HDL-c levels (34.4 % and 12.5 % respectively, \( P<0.001 \)) compared to pre-treatment levels (table 2). Table 2 also showed that LDL-c levels were significantly decreased in patients treated with captopril or losartan with glibenclamide (31.8% and 14% respectively, \( P<0.01 \)) compared to pretreatment levels. Non-significant decrease (3.5%) was reported when placebo formula was added to the currently used oral hypoglycemic agent. Table 3 showed that after 4 months no significant changes were reported in blood urea levels (9%) in placebo-treated group (group A), while treatment of diabetic patients with 12.5 mg captopril or 25 mg losartan with glibenclamide for 4 months resulted in a significant reduction in blood urea (18% and 16.7% respectively, \( P<0.01 \)). Meanwhile, adjunct use of captopril or losartan with glibenclamide resulted in a significant reduction in serum creatinine (25% and 20% respectively, \( P<0.05 \)) after 4 months compared to placebo-treated group (group A), which showed no changes in serum creatinine after 4 months. Table 3 also showed that group A patients demonstrated continuous elevation in microalbuminuria, the other parameter which gives an idea about renal function, after 4 months; while groups B and C patients showed significant reduction in microalbuminuria (32.8% and 32.3%, \( P<0.01 \)), compared to pre-treatment levels.

The data presented in table 4 showed that in patients group A no significant changes were reported in liver function after 4 months; however, a significant elevation in SGOT activity was reported due to the use of 12.5 mg captopril or 25 mg losartan with glibenclamide (35.8% and 41.3%, \( P<0.05 \)) after 4 months compared to pretreatment levels but enzyme activity was still within the normal values. Table 4 also showed that the percent changes in SGPT activity in group A patients were non-significantly changed during 4 months treatment, while there was a significant elevation in SGPT activity after 4 months treatment with captopril or losartan (36.8% and 43.5% respectively, \( P<0.05 \)) compared to pretreatment levels. ALP activity in the serum was non-significantly changed in the three groups (-2.5%, 11.5%, 12.3% respectively, \( P>0.05 \)) after 4 months treatment. Concerning the effect on GGT activity, in group A there was a small non significant change reported after 4 months treatment with placebo formula; while significant elevation (\( P<0.01 \)) was reported in both groups (B and C) after 4 months of treatment with captopril (51.4%) or losartan (54.1%) respectively, compared to pretreatment levels (table-4).

**Discussion:**

Cross-talk between the rennin-angiotensin system (RAS) and insulin signaling has been demonstrated \([25]\), and the inhibition of RAS by ACEIs or AT1 antagonists (ARBs) has been shown to both increase insulin sensitivity and
improve endothelial function\cite{26,27}. In the present study, significant reduction in FPG was reported in patients treated with captopril, in addition to glibenclamide, compared to those treated with the oral hypoglycemic agent alone; and this result was compatible with that reported by Banglore et al. (2007), where the use of ramipril in therapeutic doses, in patients with impaired fasting glucose or impaired glucose tolerance, significantly increase regression to normoglycemia\cite{28}. Moreover, it has been concluded that infusion of angiotensin II in rats, in a doses that increase blood pressure, increases a steady state of insulin resistance due to reduced glucose utilization because of vasoconstriction or increased hepatic glucose production, with consequent elevation of blood glucose level\cite{29}. More evidences have been provided by Torlone et al. (2007), where administration of captopril in hypertensive patients with type 2 DM resulted in more suppressed hepatic glucose production and greater glucose utilization due to improved insulin sensitivity both in hepatic and extra-hepatic tissues\cite{30}. The present study also showed that adjunct use of losartan, AgII receptor blocker, with the oral hypoglycemic agent in type 2 DM patients significantly decreased fasting blood glucose levels, and this observation was compatible with that reported by Hui-Min et al. (2007), who indicate that administration of losartan, in relatively high therapeutic doses, in DM patients with nephropathy significantly reduces fasting blood glucose levels, mostly due to an increase in insulin sensitivity and improving glucose homeostasis\cite{31}. Additionally, it has been suggested that the plasma glucose-lowering activity of ARBs was associated with an increase in glucose utilization by peripheral tissues and/or reduction in hepatic gluconeogenesis in the absence of insulin\cite{32}. The rennin-angiotensin system (RAS) may have a direct role in the pathogenesis of diabetes, where Angiotensin II-mediated increase in oxidative stress, inflammation and free fatty acids concentrations potentially contribute to β-cell dysfunction in diabetes. Additionally, activation of RAS appears to potentiate the action of other pathogenic pathways, including glucotoxicity, lipotoxicity and advanced glycation\cite{33}. Accordingly, blocking this system or limiting its activation with ACEIs or ARBs will augment the effects of drugs used to treat diabetes and targeting other pathways, the case that we evaluate in the present study. In experimental model of type 2 diabetes, blockade of RAS with ACEIs or ARBs also results in the improvement of islet structure and function\cite{34}. Since improvements in structural parameters were also associated with functional improvements in first-phase insulin secretion, this may provide a possible mechanism for the reduced incidence of new-onset diabetes by RAS blockade\cite{35}. Meanwhile, ARBs appeared to prevent diabetes in heart failure patients, suggesting that RAS is implicated in glucose homeostasis\cite{36}. The present study showed that there is a significant difference in FPG between the patients treated with captopril and those treated with losartan, and
this finding is compatible with the observations of Nakagawa et al. (1999), who demonstrated that quinalapril improves insulin sensitivity more effectively than losartan in genetically hypertensive rats with insulin resistance, and this may be attributed to the role of endogenous kinins[^37], where ACEIs block the breakdown of bradykinin, which lead to increase the production of nitric oxide (NO) that contributes to the augmented endothelium-initiated vasodilatation[^38,39].

The present study showed significant decrease in HbA1c levels after 4 months of treatment with a combination of captopril or losartan with glibenclamide compared to those treated with glibenclamide alone; HbA1c levels provide an indication for the average control of blood glucose during 2-3 months in both pre- and post-prandial states; since captopril improves tissue sensitivity to insulin, the consequent long term events will be a decrease in HbA1c levels[^40].

The present finding is compatible with that reported by Hiromichi et al. (2003), where captopril decreases HbA1c level in diabetic patients with nephropathy[^41]. Similarly, this observation is found compatible with that reported by Hui-Min et al. (2007), where therapeutic doses of losartan decreased HbA1c levels in diabetic patients with nephropathy[^42]. Both captopril and losartan improve the capacity of β-cells to secrete insulin, and table 1 reflects this effect through the significant elevation in C-peptide levels in patients treated with low doses of captopril or losartan in addition to the currently followed therapeutic regimen; such effect might be one of the explanations for the improvement in the glucose homeostasis reported in the present study; such finding is compatible with the observation of Hui-Min et al. (2007), where losartan affect C-peptide levels and insulin sensitivity index after 3 months treatment[^42].

The present study revealed also a significantly greater improvement in the lipid profile of diabetic patients treated with captopril or losartan compared to those treated with the oral hypoglycemic agent alone; this might be attributed to the interference with the local rennin-angiotensin system in the skeletal muscles, which affect exercise performance and carbohydrate metabolism in this site[^43]. Additionally, the concept that local rennin-angiotensin system plays a role in body-fat storage, and in lipid and carbohydrate metabolism is further supported by many studies, and revealing that susceptibility to weight gain and possibly insulin resistance is greater in individuals carrying certain allelic variants of rennin-angiotensin system associated with alterations in systemic and local angiotensin levels and ACE activity, with consequent impairment in insulin sensitivity and lipid metabolism at many sites[^44]. It has been reported that ACEIs and ARBs improve sensitivity of tissues to the effect of insulin[^45], since hypoglycemia is a major cause and/or consequence of impaired insulin effect[^46], the effects of captopril and losartan on lipid profile can be explained accordingly.
Interference with RAS in diabetic patients significantly improves renal function (table-3), even in the low doses regimen utilized in the present study; this effect is compatible with the previously reported data in this respect, where relief from intra-renal over activity of RAS by strict control of blood glucose and/or RAS inhibition is found important for improving renal haemodynamics, and provide an evidence about the beneficial effects of ACEIs and ARBs in diabetic patients\[47,48\].

Finally, the effects of captopril and losartan in producing slight elevation in the serum levels of liver enzymes activity might be related to their relatively extensive metabolic inactivation in the liver, with consequent elevation of their activities in the serum\[49\].

In conclusion, interfering with the exaggerated rennin-angiotensin system in type 2 DM patients might be one of the therapeutic targets that could be utilized for glycemic control.

Acknowledgment:
The authors gratefully thank University of Baghdad for supporting the study and the National Center for Diabetes for clinical assistance.

References:


37 - Nakagawa, H.; Daihara, M. and Tamakawa, H. et al. (1999). Effects of Quinapril and Losartan on Insulin Sensitivity in Genetic Hypertensive Rats


Table-1: Effect of Treatment with 12.5 mg/day Captopril, 25 mg/day Losartan on Fasting Plasma Glucose (FPG), Glycated Hemoglobin (HbA1c), C-peptide Levels in Type 2 Diabetic Patients.
Values were expressed as mean ± SEM; n =number of patients; * Significantly different compared to baseline value (P<0.05); Values with non identical superscripts (a,b,c) within the post-treatment data were considered significantly different (P<0.05).

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>n</th>
<th>Duration</th>
<th>FPG mg/dl</th>
<th>HbA1c %</th>
<th>C-peptide ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Group A Placebo + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>194.7 ± 15.3</td>
<td>8.2 ± 0.4</td>
<td>0.53 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>190.5 ± 13.7 a</td>
<td>8.3 ± 0.3 a</td>
<td>0.56 ± 0.12 a</td>
</tr>
<tr>
<td>*Group B Captopril + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>191.4 ± 15.2</td>
<td>8.1 ± 0.3</td>
<td>0.56 ± 0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>132.6 ± 5.3 b</td>
<td>6.4 ± 0.2 b</td>
<td>1.33 ± 0.13 b</td>
</tr>
<tr>
<td>*Group C Losartan + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>190.7 ± 10.6</td>
<td>8.0 ± 0.13</td>
<td>0.54 ± 0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>176.6 ± 12.0 c</td>
<td>7.6 ± 0.15 c</td>
<td>1.03 ± 0.1 c</td>
</tr>
</tbody>
</table>

Table-2: Effect of Treatment with 12.5 mg/day Captopril, 25 mg/day Losartan on Total cholesterol (TC), Triglyceride (TG), High density lipoprotein (HDL-c) and Low density lipoprotein (LDL-c) Levels in Type 2 Diabetic Patients.
Values were expressed as mean ± SEM; n =number of patients; * Significantly different compared to baseline value (P<0.05); Values with non identical superscripts (a,b,c) within the post-treatment data were considered significantly different (P<0.05).

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>N</th>
<th>Duration</th>
<th>T.C mg/dl</th>
<th>TG mg/dl</th>
<th>HDL-c mg/dl</th>
<th>LDL-c mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Group A Placebo + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>225.6 ± 16</td>
<td>206 ± 6.0</td>
<td>38 ± 1.9</td>
<td>141 ± 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>222.5 ± 11.9 a</td>
<td>200 ± 6.0 a</td>
<td>38 ± 2.0 a</td>
<td>136 ± 11 a</td>
</tr>
<tr>
<td>*Group B Captopril + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>220.8 ± 8</td>
<td>204 ± 16</td>
<td>38.7 ± 1.3</td>
<td>142 ± 7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>175.4 ± 5 a b</td>
<td>150 ±10 b</td>
<td>52 ± 3.2 b</td>
<td>96 ± 3 b</td>
</tr>
<tr>
<td>*Group C Losartan + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>222 ± 8</td>
<td>201 ± 10</td>
<td>40.8 ± 1.7</td>
<td>145.5 ± 8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>187.2 ± 6.6 b</td>
<td>178 ± 9 c</td>
<td>45 ± 3 c</td>
<td>125 ± 7 c</td>
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</table>
Table-3: Effect of Treatment with 12.5 mg/day Captopril, 25 mg/day Losartan on renal function [Blood Urea (B.U), Serum Creatinine (S.Cr), Microalbuminuria (MAU)] Levels in Type 2 Diabetic Patients.

Values were expressed as mean ± SEM; n = number of patients; * Significantly different compared to baseline value (P<0.05); Values with non identical superscripts (a,b,c) within the post-treatment data were considered significantly different (P<0.05).

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>n</th>
<th>Duration</th>
<th>B.U mg/dl</th>
<th>S.Cr mg/dl</th>
<th>MAU mg/l</th>
</tr>
</thead>
<tbody>
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<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>34.8 ± 3.4</td>
<td>1.1 ± 0.22</td>
<td>235.5 ± 21</td>
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<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>34.5 ± 4 *a</td>
<td>1.1 ± 0.16 *a</td>
<td>244.6 ± 23 *a</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>31 ± 1.5</td>
<td>1.1 ± 0.2</td>
<td>238.3 ± 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>25.4 ± 1.4 *b</td>
<td>0.82 ± 0.1 *b</td>
<td>160.2 ± 11 *b</td>
</tr>
<tr>
<td><strong>Group C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>31 ± 1.5</td>
<td>0.96 ± 0.13</td>
<td>241.5 ± 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>25.8 ± 1.6 *b</td>
<td>0.77 ± 0.15 *b</td>
<td>163.4 ± 14 *c</td>
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</table>

Table-4: Effect of Treatment with 12.5 mg/day Captopril, 25 mg/day Losartan on Liver Enzymes Activities (SGOT, SGPT, ALP and GGT) Levels in Type 2 Diabetic Patients.

Values were expressed as mean ± SEM; n = number of patients; * Significantly different compared to baseline value (P<0.05); Values with non identical superscripts (a,b) within the post-treatment data were considered significantly different (P<0.05).

<table>
<thead>
<tr>
<th>Patients Groups</th>
<th>n</th>
<th>Duration</th>
<th>GOT U/L</th>
<th>GPT U/L</th>
<th>ALP U/L</th>
<th>GGT U/L</th>
</tr>
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<tr>
<td><strong>Group A</strong></td>
<td></td>
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<tr>
<td>Placebo + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>19 ± 1.0</td>
<td>19 ± 1.0</td>
<td>103.5 ± 6.3</td>
<td>40.5 ± 4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>19 ± 1.7 *a</td>
<td>21.9 ± 1.0 *a</td>
<td>100.9 ± 6.5 *a</td>
<td>43 ± 4.3 *a</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
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<tr>
<td>Captopril + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>19.8 ± 0.4</td>
<td>19 ± 0.67</td>
<td>101.9 ± 3</td>
<td>42.4 ± 3.4</td>
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<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>26.9 ± 0.7 *a</td>
<td>26 ± 0.8 *b</td>
<td>113.6 ± 2.5 *a</td>
<td>64.2 ± 2.4 *b</td>
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<tr>
<td><strong>Group C</strong></td>
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<tr>
<td>Losartan + glibenclamide</td>
<td>25</td>
<td>Zero time</td>
<td>18.4 ± 0.8</td>
<td>17.7 ± 0.87</td>
<td>102 ± 2.4</td>
<td>40.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 months</td>
<td>26 ± 1.0 *a</td>
<td>25.4 ± 0.89 *b</td>
<td>114.5 ± 2.0 *a</td>
<td>62.4 ± 2.0 *b</td>
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