AJPS, 2010, Vol. 8, No.2

Accepted 2 August 2009

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

Nesren Shaban Mohammed[*], Esam Noori Al-Karwi[**], Ahmed Tariq Numan[***] and Saad Abdul-Rehman Hussain[***]

[*]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad.

[**]National Center for Diabetes, Al-Mustansriya University.

[***]Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad.

الخلاصة

أثبتت الدراسات الحديثة وجود ترابط بين ظاهرة قصور افراز الأنسولين أو عدم فاعليته في تنظيم مستوى الكلوكوز في الجسم وفعالية نظام الرنين–أنجيوتنسين من خلال دوره في تنظيم جريان الدم في البنكرياس. تم تصميم هذه الدراسة لتقييم تأثير جرع قليلة من مادتي كابوتين ولوسارتان كعلاج تكميلي لحالات ضعف السيطرةعلى مستوى السكر في الجسم بواسطة خافضات السكر الفموية (مثل الكلبنكلمايد) لوحدها. تم أجراء الدراسة على 75 مريضا بالنوع الثاني من داء السكري غير المسيطر عليه بالعلاج بواسطة الكلبنكلمايد، وتم تقسيمهم عشوائيا الى ثلاثة مجموعات: الأولى (25 مريضا) تم علاجهم بجرعة تهدئة تحتوي على اللاكتوز فقط أضافة الى كلبنكلمايد 10ملغم/يوم لمدة أربعة شهور؛ المجموعة الثانية (25 مريضا) تم علاجهم بجرعة مقدارها 12،5 ملغم/يوم من مادة كابتوبريل اضافة الى الكلبنكلمايد؛ والمجموعة الثالثة (25 مريضا) تم علاجهم بجرعة مقدارها 25 ملغم/يوم من مادة لوسارتان اضافة الى الكلبنكلمايد ولمدة أربعة شهور. بعد صيام لمدة 12 ساعة، تم أخذ عينات من الدم من جميع المرضى قبل بدء العلاج وبعد أربعة شهور لقياس مستوى الكلوكوز في الدم ومستوى كلوزة خضاب الدم، الببتيد–سي، اليوريا والكرياتينين وأنزيمات الكبد (AST, ALT, ALP, GGT) في الدم كما تم جمع عينات من الأدرار لتقييم مستوى الألبومين الدقيق كمعايير لمتابعة وتقييم تأثير العلاج.

أظهرت النتائج بأن استخدام جرع قليلة من مادة كابتوبريل أو لوسارتان مع الكلبنكلمايد أدى الى انخفاض مستوى الكلوكوز وكلوزة خضاب الدم متزامنا مع زيادة في مستوى الببتيد–سي مقارنة مع المرضى الذين تم علاجهم بجرعة التهدئة، بالأضافة الى تحسين صورة الشحوم وخفض مستوى طرح الألبومين في الأدرار. من خلال هذه النتائج يمكن الأستنتاج بأن التدخل في فعالية نظام الرنين–أنجيوتنسين يزيد من حساسية انسجة الجسم لفعالية الأنسولين وكذلك تحفيز البنكرياس على زيادة أفرازه مما يؤدي الى تحسين مستوى السيطرة على مستوى الكلوكوز في الدم.

Accepted 2 August 2009

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 rennin-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 (HbA_1c), 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 Hb_{A1c} 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

Accepted 2 August 2009

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

Accepted 2 August 2009

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 (Medocheme 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) [13], glycated hemoglobin (HbA_1c) [14], triglyceride (TG) [15], cholesterol [16], low density lipoprotein (LDL-c), high density lipoprotein (HDL-c) [17], blood urea [18], serum creatinine [19], C-peptide [20], alanine transaminase, aspartat transaminase [21], alkaline phosphates (ALP) [22], gamma glutamyl transferase (GGT) [23], and microalbuminuria (MAU) [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 captpril 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 triglycerides levels were significantly decreased in patients treated with captopril 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.

Accepted 2 August 2009

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

Accepted 2 August 2009

improve endothelial function [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 [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[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 [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 [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 [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[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 [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 [35]. Meanwhile, ARBs appeared to prevent diabetes in heart failure patients, suggesting that RAS is implicated in glucose homeostasis [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

Accepted 2 August 2009

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; HbA_{1c} 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 HbA_{1c} 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.

Accepted 2 August 2009

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:

1 - Doyle, M.E. and Egan, J.M. (2003). Pharmacological Agents That Directly Modulate Insulin Secretion; Diabetes Section, National Institute on Aging, Proceeding of National Institute of Health, Baltimore, Maryland. 55(1): 105-131.

2 - American Diabetes Association: Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2006; 29: S43-S48.

3 - Van Haeften, T.W.; Pimenta, W. and Mitrakou, A. *et. al*. (2000). Relative contributions of beta-cell function and tissue insulin sensitivity to fasting and postglucose-load glycemia. *Metabolism*. 49: 1318–1325.

4 - American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* (2000); 23(1): S32-S42.

5 - Durst, S.W. (2004). Hypertension Management in the Diabetes Patient. *J Pharm Practice*. 17: 55-60.

6 - Fink, A.S.;Wang,Y. and Mendez, T. *et al*. (2002). Angiotensin II evokes calcium-mediated signaling events in isolated dog pancreatic epithelial cells. *Pancreas*. 25: 290-295.

7 - Tsang, S.W.; I.p S.P and Wong, T.P. *et al*. (2003). Differential effects of saralasin and ramiprilat, the inhibitors of renin-angiotensin system, on cerulein-induced acute pancreatitis. *Regulatory Peptides*. 111: 47-53.

8 - Kuno, A.; Yamada, T. and Kasuda, K. *et al*. (2003). Angiotensin-converting enzyme inhibitor attenuates pancreatic inflammation and fibrosis in male Wistar Bonn/Kobori rats. *Gastroenterology*. 124: 1010-1011

Accepted 2 August 2009

9 - Tsang, S.W.; I.p. S.P. and Leung, P.S. (2004). Prophylactic and therapeutic treatments with AT1 and AT2 receptor antagonists and their effects on changes in the severity of pancreatitis. *Int J Biochem Cell Biol*. 36: 330-339.

10 - Chan, Y.C. and Leung, P.S. (2006). AT1 receptor antagonism ameliorates acute pancreatitis-associated pulmonary injury. *Regulatory Peptides* 134: 46-53.

11 - Leung, P.S. and Carlsson, P.O. (2005). Pancreatic islet rennin angiotensin system: its novel roles in islet function and diabetes mellitus. *Pancreas*. 30(4); 293-298.

12 - Leung, P.S. (2007). Mechanisms of protective effects induced by blockade of the renin-angiotensin system: novel role of the pancreatic islet angiotensin-generating system in Type 2 diabetes. *Diabet Med*. 24: 110-116.

13 - Shao, J.; Iwashita, N. and Ikeda, F. *et al*. (2006). Beneficial effects of candesartan, an angiotensin II type 1 receptor blocker, on beta-cell function and morphology in db/db mice. *Biochem Biophys Res Commun.* 344: 1224-1233.

14 - Barham, D. and Trendoer, P. (1972). An improved color reagent from the determination of blood glucose by the oxidative system *Analyst.* 97: 142-145.

15 - Fassati, P. and Principe, L. (1982). Measurement of serum triglyceride colorimetrically with an enzyme that produce H_2O_2. *Clin Chem.* 28(10): 2077-2080.

16 - Richmond, W. (1974). Proceeding in the development of an enzymatic technique for the assay of cholesterol in biological fluids. *Clin Sci Mol.* 46: 6-7.

17 - Burstein, M.; Scholink, H.R. and Morfin, R. (1970). Measurement of HDL-C in the plasma with sensitive colorimetric method. *J Lipid Res.* 19: 583.

18 - Faweet, J.K. (1960). Scott JE. Determination of urea in blood or serum. *J Clin Path*. 13:156-159.

19 - Jaffe, M. (1986). Ueberden, Niederschlag welchen Pikrinsaure in normalen harn erzeugt und uber eine neue, Reaction des Kreatinins. *Physiol Chem*. 10 :391-400.

20 - Lindstrom, T. (1992). C-peptide profiles in patients with non- insulin dependent diabetes mellitus before and during treatment. *Acta Endocrinol*. 126(6): 477-489.

21 - Reitman, S. and Frankel, S. (1957). *Am J Clin Path.* 28: 56.

22 - Kind ,P.R. and King, E.J. (1954). Estimation of plasma phosphatase by determination of hydrolyzed phenol with amino-antipyrine *J Clin Path.* 7: 322-326.

23 - Tietz , N.W.; Burtis , E.R. and Ashwood, W.B. (1999). Text book of clinical chemistry, 3rd Edition; C.A. Saunders, 43: 686-689.

Accepted 2 August 2009

24 - McElderry, L.A.; Tarbit, I.F. and Cassels-Smith, A.S. (1982). Six methods for urinary protein compared. *Clin Chem*. 28: 256-260.

25 - Folli, F.; Kahn, C.R. and Hansen, H. *et al*. (1997). Angiotensin II Inhibits Insulin Signaling in Aortic Smooth Muscle Cells at Multiple Levels, A Potential Role for Serine Phosphorylation in Insulin/Angiotensin II: *J Clin Invest.* 100: 2158-2169.

26 - Paolisso, G.; Taglimonte, M.R and Gambardella, A., *et al.* (1997). Losartan-mediated improvement in insulin action is mainly due to an increase in non-oxidative glucose metabolism and blood flow in insulin resistant hypertensive patients. *J Hum Hypertens.* 11: 307-312.

27 - Henriksen, E.J.; Jacob, S. and Kinnick, T.R. *et al*. (2001). Selective Angiotensin II Receptor Antagonism Reduces Insulin Resistance in Obese Zucker Rats. *Hypertension*. 38: 884-890.

28 - Bangalore, S.; Messerli, F.H. and Potter, B.J. (2007). Effect of Ramipril on the Incidence of Diabetes. *N Engl J Med*. 356: 522-524.

29 - Rao, R.H. (1994). Effects of angiotensin II on insulin sensitivity and fasting glucose metabolism in rats. *Am J Hypertens*. *7*: 655-660.

30 - Torlone, E.; Rambotti, A.M. and Perriello, G. *et al*. (1991). ACE-inhibition increases hepatic and extrahepatic sensitivity to insulin in patients with type 2 (non-insulin-dependent) diabetes mellitus and arterial hypertension. *Diabetologia*. 34(2): 119-125.

31 - Jin, H. and Pan, Y. (2007). Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. *Nephrol Dial Transplant*; 22(7): 1943-1949.

32 - Chan, P.A.; Liu, W.K, and Min, B.C. *et. al*. (2003). Antihyperglycemic action of angiotensin II receptor antagonist, valsartan, in streptozotocin-induced diabetic rats. *J Hypert*; 21(4): 761-769.

33 - Cooper, M.; Tikellis, E. and Chris, T. *et. al.* (2006). Preventing diabetes in patients with hypertension: one more reason to block the renin-angiotensin system. *J Hypert.* 24 (1): S57-S63.

34 - DiSomma, S. and Sentimentale, A.(2006). New Onset of Type 2 Diabetes Mellitus during Antihypertensive Therapy: What Evidence? High Blood Pressure & Cardiovascular Prevention. *J Hypert.* 13(1): 29-36.

35 - Tikellis, I.C.; Wookey, P.J. and Candido,1. R. (2004). Improved Islet Morphology after Blockade of the Renin- Angiotensin System in the ZDF Rat. *Diabetes care*. 53: 989-997.

36 - Salim,Y.; Jan, B. and Ostergren, C. *et. al*. (2005). Effects of Candesartan on the Development of a New Diagnosis of Diabetes Mellitus in Patients with Heart Failure. *Circulation.* 112: 48-53.

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

Accepted 2 August 2009

with Different Metabolic Abnormalities. *J Cardiovasc Pharmacol.* 34(1): 28-33.

38 - Damas, J.; Hallet, C. and Lefebvre, P.J. *et.al*. (2001). Changes in blood glucose and plasma insulin levels induced by bradykinin in anaesthetized rats. *Br J Pharmacol*. 134(6): 1312-1318.

39 - Craig, C.; Julie, C. and Gerard, O. *et.al*. (2000). Losartan, an angiotensin type 1 receptor antagonist, improves endothelial function in non-insulin-dependent diabetes; *J Am Coll Cardiol*. 36: 1461-1466.

40 - American Diabetes Association. How do we diagnose diabetes and measure blood glucose control? *Diabetes Spectrum* (2001). 14: 71-74.

41 - Hiromichi, T.; Eiji, I. and Takahiko, K. *et.al*. (2003). Intrarenal hemodynamic changes after captopril test in patients with type 2 diabetes. *Diabetes Care*. 26: 132-137.

42 - Jin, H. and Pan, Y. (2007). Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. *Nephrol Dial Transplant*. 22(7): 1943-1949.

43 - Strazzullo, P. and Galletti, F. (2004). Impact of the renin-angiotensin system on lipid and carbohydrate metabolism. *Curr Nephrol Hyperten*. 13(3): 325-332.

44 - Ogihara, T.; Asano, T.; Ando, K. and Chiba, Y. *et. al*. (2002). Angiotensin II -induced insulin resistance is associated with enhanced insulin signaling. *Hypertension*. 40: 872–879.

45 - Frossard, M.; Joukhadar, C. and Steffen, G. *et. al*. (2000). Paracrine effects of angiotensin- converting-enzyme and angiotensin-II-receptor-inhibitior on transcapillary glucose transport in humans. *Life Sci*. 66: 147–154.

46 - Suga, A.; Hirano, T.; Inoue, S.and Tsuji, M. *et.al*. (1999). Plasma leptin levels and triglyceride secretion rates in VMH-lesioned obese rats: a role of adiposity. *Am J Physiol Endocrinol Metab*. 276: E650–E657.

47 - Matsumoto, N.; Ishimura, E. and Taniwaki, H. *et.al.* (2000). Diabetes mellitus worsens intrarenal hemodynamic abnormalities in non-dialyzed patients with chronic renal failure. *Nephron*. 86: 44–51.

48 - Hiromichi, T.; Eiji, I. and Takahiko, K. *et.al*. (2003). Intrarenal Hemodynamic Changes after Captopril Test in Patients with Type 2 Diabetes. *Diabetes Care*. 26: 132-137.

49 - Jong, P.E. and Zeeuw, D. (2007). Side Effects and Drug Interactions. *Disease and Condition*. 14: 342-345.

Accepted 2 August 2009

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

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).

Patients Groups	N	Duration	T.C mg/dl	TG mg/dl	HDL-c mg/dl	LDL-c mg/dl
Group A Placebo + glibneclamide	25	Zero time	225.6 ± 16	206 ± 6.0	38 ± 1.9	141 ± 17
		4 months	222.5 ± 11.9[a]	200 ± 6.0 [a]	38 ± 2.0 [a]	136 ± 11 [a]
Group B Captopril + glibneclamide	25	Zero time	220.8 ± 8	204 ± 16	38.7 ± 1.3	142 ± 7.6
		4 months	175.4 ± 5 [* a]	150 ±10 [* b]	52 ± 3.2 [* b]	96 ± 3 [* b]
Group C Losartan + glibneclamide	25	Zero time	222 ± 8	201 ± 10	40.8 ± 1.7	145.5 ± 8.5
		4 months	187.2 ± 6.6 [*b]	178 ± 9 [* c]	45 ± 3 [* c]	125 ± 7 [* c]

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).

Accepted 2 August 2009

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

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).

Patients Groups	n	Duration	GOT U/L	GPT U/L	ALP U/L	GGT U/L
Group A Placebo + glibenclamide	25	Zero time	19 ± 1.0	19 ± 1.0	103.5 ± 6.3	40.5 ± 4.0
		4 months	19 ± 1.7 [a]	21.9 ± 1.0 [a]	100.9 ± 6.5 [a]	43 ± 4.3 [a]
Group B Captopril + glibenclamide	25	Zero time	19.8 ± 0.4	19 ± 0.67	101.9 ± 3	42.4 ± 3.4
		4 months	26.9 ± 0.7 [*a]	26 ± 0.8 [* b]	113.6 ±2.5 [*a]	64.2 ± 2.4 [* b]
Group C Losartan + glibenclamide	25	Zero time	18.4 ± 0.8	17.7 ± .87	102 ± 2.4	40.5 ± 3.0
		4 months	26 ± 1.0 [* a]	25.4 ± 0.89 [*b]	114.5 ± 2 [* a]	62.4 ± 2.0 [* b]

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).