P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2013,(7), (3) :97-101

Antioxidant effect of Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) in Type 2 Diabetic Patients

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ARTICLE INFO

Received: 14 / 12 /2014
Accepted: 14 / 4 /2013
Available online: 19/7/2022
DOI:

Keywords:
Antioxidant ,
Angiotensin Converting Enzyme Inhibitors (ACEIs) ,
Angiotensin Receptor Blockers (ARBs) ,
Type 2 Diabetic Patients.

ABSTRACT

Free radical mediated oxidative stress is mainly involved in the pathogenesis of diabetic complications. It has been shown that angiotensin-converting enzyme inhibition or angiotensin receptor blockade may improve endothelial dysfunction, in patients with diabetes, whether this protective effect is mediated through blood pressure-lowering effects or other specific mechanisms such as a reduction in oxidative stress.The present study, was designed to evaluate the influence of captopril compared with losartan on total antioxidant status (TAS) in patients with type 2 diabetes . 75 patients with uncontrolled type 2 diabetes mellitus were included in this randomized ,double-blind study; they were divided into:25 patients received placebo formula for 4 months ,25 patients received 12.5 mg of captopril once a day for 4 months ,25 patients received 25 mg of losartan given as a single daily dose for 4 months, whereas other medication of oral hypoglycemic drug remained unchanged. At baseline and after 4 months of treatment flow-mediated for fasting blood sugar (FBS), blood pressure , glycated heamoglobin A1c (HbA1c) and plasma total antioxidant status (TAS) were measured.Statistical analysis (ANOVA) showed a significant decrease in fasting blood sugar (FBS), HBA1c ,and a significant increase in total antioxidant status (TAS) in group taking captopril or losartan in comparison to placebo group .This study demonstrated that captopril and losartan significantly improved endothelial function in type 2 diabetes patients, which must be independent of the blood pressure-lowering effect and is probably caused by an antioxidative effect of the angiotensin converting enzyme inhibitor or AT1-receptor blockade.

Introduction:

Recently, oxidative stress has been associated and increased in diabetes.(1)(2), since oxidative stress impairs insulin action, as has been demonstrated in type 2 diabetics and this impairment might be due to several factors, such as decreased availability of NO .(3) Oxidative stress occurs when free radical production exceeds the body's ability to neutralize them (4),for instance diabetes itself can direct to increased speed of the production of these endogenous free radicals and reduced antioxidant resistance, since hyperglycemia induced overproduction of superoxide and result in the generation of free radicals through several biochemical pathways (nonenzymatic glycation, and glucose autoxidation), which leads to physiological dysfunctions including depressed antioxidant defense mechanisms (5) (6) .

It is well known that an imbalance of reduced production of NO or increased production of reactive oxygen species mainly superoxide may promote endothelial dysfunction (7) .Both Angiotensin-converting enzyme inhibitors (ACEI) and AT1-receptor blockade may improve endothelial dysfunction in patients with diabetes by increasing endothelial nitric oxide availability via bradykinin-dependent endothelial nitric oxide release (8). Since both treatment strategies prevent increased inactivation of endothelial nitric oxide by oxygen radicals, and increasing the activity of the vascular antioxidant enzyme, extracellular superoxide

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dismutase.(9) It was shown that all sulfhydryl (-SH)-containing angiotensin-converting enzyme (ACE) inhibitors were effective scavengers of nonsuperoxide free radicals, also inhibited microsomal lipid peroxidation ,(10) in addition it induce enhancement of endogenous antioxidant defenses and include new data on glutathione-dependent defenses (11). The relative glycaemic effects of drugs within the ACE-I and ARB classes remain unclear but the data showed that ACE-Is that included a sulfhydryl group, such as captopril, may be more potent insulin sensitizers than those without it.(12)

Materials and Methods:

Double blinded, placebo-controlled clinical study was conducted on 75 uncontrolled type 2 diabetic patients, (43 male and 32 female) , with age range (35-60 years) during the period that extended from April 2012 to August 2012 , diagnosis was made under the consultant physician ,assistant professor ,at the national center of treatment and research for diabetes /Al-mustansiriya university /Baghdad, some patients excluded from the study either because of non compliance or can not reach the center due to logistic traffic obstruction .All patients were already treated with the ordinary hypoglycemic agent (glibneclamide)),but with poor glycemic control as evidenced by abnormal values of fasting serum glucose and glycated hemoglobin . Patients were informed previously that they will participate in the study and their consent was obtained ,patients selection and enrollment in the study was performed according to the fallowing inclusion criteria :They should not have other prominent associated chronic disease ,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 diabetic patients were randomized into three groups: Group A: include 25 patients treated with placebo formula containing . Group B: include 25 patients treated with 12.5 mg captopril tablets, given once daily at bed time . Group C: include 25 patients treated with 25 mg losartan tablets, given as a single daily dose at bed time, all were taken 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 that include measurement of blood pressure, fasting blood sugar, (FBS), which was measured spectrophotmetrically using a ready made kit according to the method of Barham and Trindoer(1972)[13],glycated hemoglobin (HbA1c) was evaluated using a colorimetric assay utilizing a ready kit for this purpose [14], and total antioxidant status.

Determination of total antioxidant status (TAS) in serum:

It is a colorimetric method described by Miller, NJ et al [15]. ABTs (2,2–Azio-di-[3-ethylbenzthiazoline sulphonate) is incubated with a peroxidase (metmyoglobin) and H2O2 to produce the radical cation ABTS .+ , this has a relatively stable blue-green color, which is measured at 600nm. Antioxidants in the added sample cause suppression of this color production to a degree which is proportional to their concentrations. According to the following equations:

$$HX - Fe3 + H2O2 \rightarrow X\text{-}[Fe4 = O] + H2O$$

$$ABTs + X\text{-}[Fe4 - O] \rightarrow ABTS.+ + HX - F$$

Results:

The biochemical particulars of the study subjects including NIDDM given in table (1), the subjects with diabetes had duration of the disease ranged from 5 – 10 years. They all were being treated with antihyperglycemic drugs, despite of their treatment, they had hyperglycemia blood glucose level .There was a small non-significant change in FBS after 4 months treatment with placebo from (219.7±15.3 mg/dl) to (221.4± 13.7mg/dl), while there was a significant reduction ($P<0.01$) in FBS (226.3±15.2 mg/dl) of patients treated with captopril for 4 months (134.6± 5.3mg/dl), and also a significant decrease ($P<0.05$) was observed in FBS after treatment with losartan from (222.7± 10.6 mg/dl) to (176.6±1.2 mg/dl) as shown in table (1) , the percentage change in FBS for control is only -0.8, while it was 40.5 % of patients treated with captopril and 20.7 % of patients treated with losartan . There was no significant change in HbA1c after 4 months of group A, but HbA1c showed a significant decrease ($P<0.01$)(7.1%) compared to pre-treatment (8.8%, $P<0.01$) for patients treated with captopril, and a significant change in HbA1c after 4 months of treatment of patients taking losartan (8.5% to 7.6%, $P<0.01$) as shown in table (1) ,shows the percentage changes in HbA1c before and after treatment in which there was a slight but not detectable change of patients taking placebo (-1.2 %), and the percentage change of HbA1c was (19.3%, 10.6%) in captopril and losartan groups respectively. The data showed that there was no significant change in TAS levels of placebo group, while captopril group showed a significant increased ($p<0.01$) in TAS of patients treated with captopril from (0.84 to 1.33 mmol/L) , and a significant increase in TAS in losartan group (0.8 to 1.05 mmol/L) ,the percentage changes were reported of patients treated with captopril

and losartan were as fallow (54.7% and 31.3%) respectively

Discussion:

This study regarding the potential antioxidant effect of ACE inhibitors and angiotensin-receptor blockers ,it indicated the possible role of oxidative stress in the pathogenesis of DM which is responsible for damage and dysfunction of the endothelium vessels, and examined the changes in antioxidants and oxidant status in diabetes type 2 patients (NIDDM).

Our data show that the FBS in patients taking captopril or losartan was significant lower after 4 months in comparison to placebo group and this was an agreement with(16) who showed reduction in the risk of diabetes in subjects receiving ACE inhibitors, as well as in those receiving angiotensin-receptor blockers since ACEIs improve insulin sensitivity(17) ,which may related to its effect in blocking the breakdown of bradykinin thus leading to increase the production of nitric oxide (NO)(18). Bradykinin is a powerful vasodilator and modulator of several hormone actions, including insulin and it promote the glucose flux through insulin signaling pathway as shown in figure(1) (19).

Table (1): Effect of treatment with 12.5 mg/day Captopril, 25 mg/day Losartan on fasting blood sugar (FBS), glycated hemoglobin (HbA1c), total antioxidant status (TAS) in type 2 diabetic patients.

Groups	n	Duration	FBS (mg/dl)	HbA1c %	TAS(mmol/L)
Group A	25	Zero time	219.7 ± 15.3	8.6 ± 0.4	0.89 ± 0.1
		4 Months	221.4±1 3.7[a]	8.7 ± 0.3 [a]	0.87 ± 0.12 [a]
Group B	25	Zero time	226.3.4 ±15.2	8.8 ± 0.3	0.86 ± 0.15
		4 Months	134.6± 5.3*[b]	7.1± 0.2*[b]	1.33 ± 0.13* [b]
Group C	25	Zero time	222.7 ± 10.6	8.5 ± 0.13	0.8 ± 0.13
		4 Months	176.6 ± 12*[c]	7.6±0.1 5*[c]	1.05 ± 0.1*[c]

Group A: patients treated with placebo.
Group B: patients treated with 12.5 mg Capoten
Group C: patients treated with 25 mg Losartan.
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 ($p<0.05$).

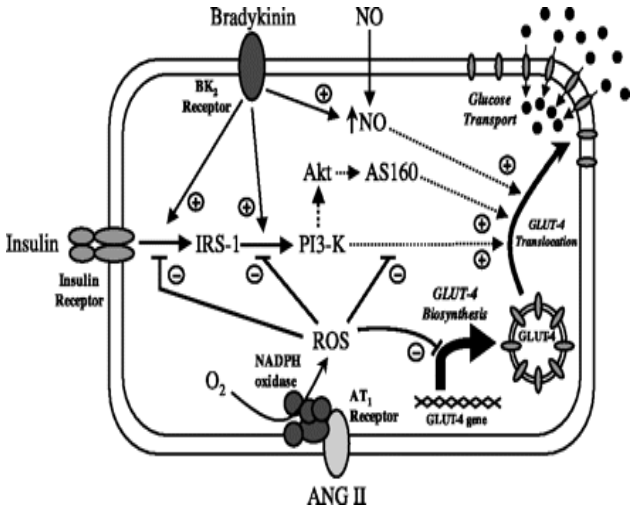

Figure (1). Modulation of insulin signaling pathway and glucose transporter GLUT-4 biogenesis by ANG II and bradykinin in skeletal muscle cells[20].

In addition our results showed a significant decrease in HbA1c in diabetes patient after 4 months of treatment with captopril or losartan , both inhibit the effect of ANG II. ANG II is a powerful vasoconstricting hormone with specific negative effects on insulin action,[21] it can inhibit insulin induced nitric oxide (NO) production and enhances the activity of NADPH oxidase that leads to an increased reactive oxygen species generation,[22] thus ACE inhibitors are a widely used antihypertensive intervention with insulin-sensitizing actions [23].The differences in glycemic control obtained by the addition of either ACEI or ARB ,might be related to the differences in their structures, where captopril contain sulphehydryl group in its structure which assisted insulin homeostasis, redox balance and protein expression [24] that elicits beneficial metabolic effects on the hyperinsulinemia, dyslipidaemia, glucose intolerance and insulin resistance. [25]

A significance difference in the mean plasma concentration of total antioxidant status was observed in NIDDM patients before and after captopril or losartan intake and this is agreement with Argani [26] who stated that TAS increase after 4 months receiving ACEI or ARB where as Flammer[27] who also demonstrated that losartan significantly improved endothelial function in

type 2 diabetes patients , that may be independent of the blood pressure-lowering effect of losartan and is probably caused by an antioxidative effect of the angiotensin receptor blocker. The significant increase in TAS concentration in comparison to losartan indicated the antioxidant effect of ACEI with sulfhydryl group which reduce oxidative stress and improve the NO pathway [(28)(29)] . From the clinical standpoint, the inhibition of the renin angiotensin system improves insulin sensitivity and decreases the incidence of (T2DM). This study suggests that diabetes is an altered metabolic state of oxidation-reduction and that it is convenient to give therapeutic interventions with antioxidants.

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تاثير مضادات الاكسدة في مثبطات الانزيم محول الانجيوتينسين و موقفات مستلمات الانجيوتنسين في مرضى السكري من النوع الثاني

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الخلاصة

ان وجود الجذور الحرة يزيد من ألأجهاد ألتأكسدي المسبب بشكل رئيسي في مضاعفات مرض السكري وقد تبين ان تثبيط الأنزيم المحول للانجيوتنسين أوغلق مستقبلات الأنجيوتنسين قد يحسن من ضعف بطانة الأوعية الدموية في المرضى الذين يعانون من مرض السكري ، و ما إذا كان هذا التأثير الوقائي من خلال تأثيره في خفض ضغط الدم أو آليات معينة أخرى مثل الحد من الاجهاد التأكسدي. صممت هذه الدراسة لتقييم تأثير جرع قليلة من كابتوبريل مقارنة مع اللوسارتان على مضادات الأكسدة في المرضى الذين يعانون من مرض السكري من النوع الثاني . هذه الدراسة العشوائية شملت 75 مريضا يعانون من داء السكري النوع الثاني غير المنضبط، تم تقسيمهم الى ثلاث مجموعات :المجموعة الأولى 25 مريضا تلقو جرعة وهمية من اللاكتوز لمدة اربعة اشهر ،المجموعة الثانية: 25 مريضا تلقو جرعة مقدارها 12.5 ملغم /يوم من مادة الكابتوبريل لمدة اربعة اشهر ،المجموعة الثالثة:25 مريضا تلقو 25 ملغم/ يوم لمدة اربعة اشهر، في حين استمرت الأدوية المستخدمة الأخرى من مخفضات السكري دون تغير وتم اخذ عينات من الدم من جميع المرضى قبل البدء بالعلاج وبعد اربعة اشهر لقياس مستوى الكلوكوز في الدم ،ضغط الدم ، مستوى كلوكوز خضاب الدم وتم قياس المواد المانعة للتأكسد . اظهر التحليل الإحصائي انخفاض ملحوظ في مستوى الكلوكوز وكلوكوز خضاب الدم متزامنا مع ارتفاع في تركيز موانع الأكسدة في المرضى الذين استلموا الكابتوبريل او اللوسارتان بالمقارنة مع المرضى الذين تلقوا الجرعة الوهمية. أظهرت هذه الدراسة أن كابتوبريل واللوسارتان قد أظهرا تحسنا ملحوظا في وظيفة بطانة الأوعية الدموية في مرضى السكري من النوع الثاني، والتي يجب أن تكون مستقلة عن تأثيرهما في خفض ضغط الدم وربما بسبب تأثيره المضاد للأكسدة من قبل مثبط الأنزيم المحول للانجيوتنسين ومغلق مستقبلات الأنجيوتنسين