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Effects of Sub therapeutic Doses of ACE-I in Improving insulin sensitivity in Type II DM Patients

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ABSTRACT

Thirty patients selected with uncontrolled non insulin dependent diabetes mellitus (NIDDM) .Their average age was (44.34 ± 7.15) years and their duration of diabetes was 8.48 ± 8.27 years, examination and selection of patients done by the consultant physician ,assistant professor ,at the national center of treatment and research for diabetes .Essential kidney disease and hypertensive patients were excluded, we tested their blood pressure, fasting blood sugar (FBS),post postprandial glucose excursion (PPGE) and albuminuria before and after daily captopril intake for 2 months The results showed a significant decrease (p<0.01) in PPGE (postprandial glucose excursion) , after taking angiotensin converting enzyme (ACE) inhibitor captopril mean (185 ± 28.75 mg/dl) when compared before captopril intake (230 ± 45 mg/dl) , when calculating the area under the curve. In which these results indicated a positive effect of captopril on insulin sensitivity and blood glucose level.

Introduction:

Diabetes mellitus (DM) is a chronic condition that is diagnosed by a blood test and requires life-long management ⁽¹⁾ .DM is a complex, multifactorial and heterogeneous group of disorders characterized by endogenous insulin deficiency and/or insulin resistance. While Beta cell failure results in inadequate circulating insulin levels (as in type 1 and type 2) ⁽²⁾. *Type 1 DM* is characterized by little or no endogenous insulin production. These patients require exogenous insulin, tend to be diagnosed before age 30, *Type 2 DM* is usually diagnosed after age 30. where a decrease in the number of insulin receptors, or decreased insulin production by chronically stressed pancreatic beta cells. ⁽³⁾

The glycemic index of the meal depends on the nature of the ingested food and starch composition, thus one of the important test is Postprandial blood glucose excursion (PPGE). In healthy controls, hepatic glucose production is halved after a meal; the nature of the starch was found to be an important determinant of the blood glucose and insulin responses to food giving rise to the concept of glycemic index.⁽⁴⁾ However Insulin sensitivity may be influenced by activity of the renin–angiotensin system (RAS), thus drugs which inhibit the generation of angiotensin II (angiotensin-convertingenzyme inhibitors) may increase hypoglycaemia in diabetes patients ⁽⁵⁾. It has been shown that treatment with angiotensin converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB) may improve insulin sensitivity ⁽⁶⁾ and prevent the development of type 2 diabetes ^(7,8).

It has also been suggested that blockade of RAS with either ACE-i or ARB increases adiponectin production $^{(9)}$.

Subjects:

30 patients selected with type 2 DM, (21 male and 9 female) ,during the period that extended from January 2012 to March 2012, their average age was (44.34±7.15) years and their duration of diabetes was (8.48±8.27) years. The diagnostic will done under the consultant physician ,assistant professor ,at the national center of treatment and research for diabetes /Almustansiriya university /Baghdad,(in which there is filing system and regular follow up of patients by same physician to examine them clinically and reevaluate their laboratory investigation which included FBS,HbA1C,lipid profile,blood urea and creatinine,serum uric acid). Essential kidney disease and

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hypertensive patients were excluded, all patients were informed previously that they will participate in the study and their consent was obtained, some patients excluded from the study either because of non compliance or can not reach the center due to logistic traffic obstruction, the others continue the follow up for regular examination and to receive their ration of free charged drugs from the center.

Methods:

First, the patients' sex, age, duration of diabetes, history of smoking, history of another disease or any medication other than hypoglycemic drugs taken and whether they had diabetic retinopathy or not were investigated. Then blood pressure, FBS, PPGE and macroalbuminuria (MAU) were measured. Blood sugar was evaluated spectrophotmetrically using a ready made kit for this purpose according to the method of Barham and Trindoer(1972)⁽¹⁰⁾, while the MAU was determined by using a ready made kit according to Mc.Elderry⁽¹¹⁾.

To make the postprandial glucose excursion (PPGE)^{.(12)}, the patients were taken their medication to control the blood sugar, and took the basement sample (FBS), then standard meal were given to them that contain 560 Kcal energy ,then sample where taken after 30,60,90,120,170,210 min. The ACE inhibitor medication was started (captopril 12.5 mg) for 2 months to prove whether it has a hypoglycemic effect or not .The dosage was adjusted according to their blood sugar and blood pressure.

Statistical analysis

The area under the curve concentration was used to see the difference before and after the treatment, in addition to SPSS software (version 13.0 for Windows) to do test on all enumeration data. Also single factor correlation analysis to the clinical parameters was used and then multifactor correlation analysis to parameters was done to get statistical significance after single factor analysis.

RESULTS: The present study, aimed to examine whether angiotensin converting enzyme inhibitor (ACE) inhibitor, can alter insulin action and if these changes are reflected in interstitial insulin.

Our data show a significant decrease in PPGE (postprandial glucose excursion) level, after taking (ACE) inhibitor captopril mean (185 ± 28 mg/dl) then before (230 ± 45 mg/dl), when calculated by area under the curve as shown in table (1) and figure (1).

In addition, the data presented in table (1) showed that there is a small non-significant change in FBS after 2 months treatment with placebo from (188.6 $\pm 12 \text{ mg/dl}$) to (191.3 $\pm 22 \text{ mg/dl}$),indicating poor glycemic control of patients using full dose of glibenclamide. While there is a significant reduction in FBS from (192.6 $\pm 3 \text{ mg/dl}$) in patients treated with captopril for 2 months to (145.7 $\pm 42 \text{ mg/dl}$) (P<0.01),as shown in table (1).

Also a significant decrease (P<0.001) in MAU after 2 months treatment with captopril (231.4 $\pm 21 \text{mg/dl}$), (174.8 $\pm 15 \text{ mg/dl}$) respectively while no significant change in MAU in placebo, which indicates the efficacy of captopril in improving renal function ,as measured by MAU,that shown in table (1).

Table (1): Effect of Treatment with 12.5 mg/day Captopril, on Fasting Serum Glucose (FBS), PPGE and MAU in Type 2 Diabetic Patients.

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|--------------------------------|----|--------------|---------------|----------------|----------------|
| Group | u | Duration | FBS(mg/dl) | PGE(mg/dl) | MAU(mg/dl) |
| placebo | 10 | Zero time | 188.6 ±12 | 237 ±21 | 230.2 ±13 |
| | | 2 months | 191.3 ±22 | 240 ±31 | 234.6 ±24 |
| Captopril | 20 | Zero time | 192.6 ±3 | 230 ±45 | 231.4 ±21 |
| | | 2 months | 145.7 ±42* | 185 ±28 | 174.8±1 5** |

* = significant difference at level p<0.01. ** =significant difference at level p<0.001.



Figure (1): show PPGE before and after the use of captopril drug

Discussion:

Our results in a this study indicate a positive effect of captopril on insulin sensitivity and glucose metabolism.

Insulin sensitivity may be influenced by activity of the renin-angiotensin system (RAS), although the nature of this relationship remains unclear. Angiotensin II (AII), acting via its G-protein linked receptor, is an important regulator of cardiac, vascular, and renal function. AII-induced phosphorylation leads to binding of phosphatidylinositol 3-kinase (PI 3-kinase) to Insulin Receptor Substrate-1 (IRS-1) and Insulin Receptor Substrate-2 (IRS-2); the latter occurs without any reduction in insulin receptor or IRS phosphorylation. These effects of AII are inhibited by angiotensin I (AT1) receptor antagonists. Thus, there is direct crosstalk between insulin and AII signaling pathways at the level of both tyrosine phosphorylation and PI 3-kinase activation. These interactions may play an important role in the association of insulin resistance.⁽¹³⁾

Patients who start antihypertensive treatment with a captopril-based regimen may be at significantly lower risk for developing diabetes ⁽¹⁴⁾, and this is in agreement with our results

ACE inhibitors have beneficial effects on insulin sensitivity since they have the additional property of decreasing insulin resistance, which can mean improved glycemic control, it related to an increase in capillary insulin transport secondary to vasodilatation with increased capillary area is reflected in greater insulin sensitivity and in increased risk of hypoglycemia Insulin resistance of both muscle and liver has been shown to be reduced by kinins and ACE inhibitors, resulting in lowering of blood glucose concentra $tion^{(15)}$. Another theory is that using the highly potent, specific, long-acting bradykinin B2 receptor antagonist Hoe 140, showed that the potentiating of endogenous kinins can contribute to the antihypertensive action of ACE inhibitors, thereby improving glucose metabolism. Also it was demonstrated that the decrease in insulin and lipid levels induced by the ACE inhibitor was highly dependent on the accumulation of bradykinin.⁽¹⁶⁾

While another study showed that ACE inhibitors and ARBs were associated with reductions in the incidence of newly diagnosed diabetes by 27% and 23%, respectively ⁽¹⁷⁾.

And this is in agreemwnt with <u>Shorr RI</u>⁽¹⁸⁾ who prove that the rate of serious hypoglycemia was highest among those who use an antihypertensives drug of ACE inhibitors.^(19, 20, 21)

The reduced incidence of diabetes in patients at high risk of developing diabetes by ACE inhibitors has been explained by hemodynamic effects, such as improved delivery of insulin and glucose to the peripheral skeletal muscle, and non-hemodynamic effects, in-

cluding direct effects on glucose transport and insulin signaling pathways, all of which decrease insulin re-sistance. ⁽²²⁾ There is now evidence that the pancreas may contain an in situ active RAS, which appears to be up regulated in an animal model of type 2 diabetes. Thus, ACE inhibitors may act by attenuating the deleterious effect of angiotensin II on vasoconstriction, fibrosis, inflammation, apoptosis and [beta]-cell death in the pancreas, thereby protecting a critical [beta]-cell mass essential for insulin production. An evidence is presented that ACE inhibitors may delay or prevent the development of insulin resistance and diabetes (23). And this may be attributed to that captopril improve insulin sensitivity in Type 2 diabetes associated with hypertension at the level of the liver and extrahepatic tissues, primarily muscle and adipose tissue. Thus ACE-inhibitors appear to improve insulin action in Type 2 diabetes. ⁽²⁴⁾

Referaces:

- 1-Paul Chous, O.D.The New Fundamentals of Diabetes, As the public health crisis of diabetes grows, optometrists must accept their necessary role on the diabetes .health-care team, Optometric Study Center,Medical Dissertations. 2005;87(10):15-18.
- 2-Stina Lindmark from the Department of Public Health and Clinical Medicine, Mechanisms in Insulin Resistance and Type 2 Diabetes Medicine,Sweden Neurohormonal .2004;67:90-94.
- 3- HAROLD E. LEBOVITZ, ; Treating hyperglycemia in type 2 diabetes: New goals and strategies CLEVELAND CLINIC JOURNAL OF MEDI-CINE .2002;69(10):46-52.
- 4-H. GIN (1), V. RIGALLEAU (1); POST-PRANDIAL HYPERGLYCEMIA. POST-PRANDIAL HYPERGLYCEMIA AND DIABE-TES: Diabetes & Metabolism .2000; 26:265-272.
- 5-Morris, A. D., Boyle, D. I., McMahon, A. D. et al. ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside, Scotland. Medicines Monitoring Unit. Diabetes Care 1997;20, 1363–1367.
- 6-Top C, Cingozbay BY, Terekeci H, Kucukardali Y, Onde ME, Danaci M: The effects of valsartan on insulin sensitivity in patients with primary hypertension. J Int Med. Res .2002;30:15-20.
- 7- Gerstein HC: Reduction of cardiovascular events and microvascular complications in diabetes with ACE inhibitor treatment: HOPE and MICRO-HOPE. Diabetes Metab. Res Rev. 2002;18 (3):82-85.
- 8- McFarlane SI, Kumar A, Sowers JR: Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. Am J Cardiol. 2003; 91:30-37.

adiponectin concentrations in patients with essential hypertension. Hypertension .2003;42:76-81.10-Barham D,Trendoer P.An improved color reagent from the determination of blood glucose by the ox-

idative system. Analyst .1972;97:142-145.

- 11-Mc Elderry LA,Tarbit IF,Cassels AS.Six methods for urinary protein compared.Clin Chem.1982;28:256-260.
- 12-Avidnon.A,Radance.A,Monnier.L: Non fasting blood glucose is better marker of diabetic control than fasting plasma glucose in type II diabetes ; D.Care :1997;20:1822-1826.
- 13- L A Velloso, F Folli, X J Sun, et al : Cross-talk between the insulin and angiotensin signaling systems. Proc Natl Acad Sci U S A. 1996;93(22): 12490–12495.
- 14- Keely S. Solomon, Ph.D. Development of diabetes is retarded by ACE inhibition in hypertensive patients--a subanalysis of the Captopril Prevention Project (CAPPP). J Hypertens .2004 ;22(3):645-652.
- 15-Talma Rosenthal; Yael Erlich; Eliezer Rosenmann; et,al: Effects of Enalapril, Losartan, and Verapamil on Blood Pressure and Glucose Metabolism in the Cohen-Rosenthal Diabetic Hypertensive Rat. Hypertension. 1997;29:1260-1264.
- 16-Erlich Y, Rosenthal T. Contribution of bradykinin (BK) to the beneficial effects of CEI in fructose induced hyperinsulinemic rat. International Society of Hypertension; 1996; 77;855-857.
- 17- Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or an-

giotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005;46(5):821-826.

- 18-Shorr RI, Ray WA, Griffin MR. Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. JAMA. 1997; 278(1):40-43.
- 19-Chan JC, Cockram CS, Critchley JA. Drug-induced disorders of glucose metabolism. Mechanisms and management. Drug Saf. 1996;15(2):135-157.
- 20- Chelliah A, Burge MR; Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. Drugs Aging. 2004;21(8):511-530.
- 21- Zanella MT, Kohlmann O Jr, Ribeiro AB. Treatment of obesity hypertension and diabetes syndrome. Hypertension. 2001;38(3-2):705-708.
- 22-Klaus Rave 1, Sabine Flesch 1, W. Nikolaus Kühn-Velten,et,al; Enhancement of blood glucose lowering effect of a sulfonylurea when coadministered with an ACE inhibitor: results of a glucose-clamp study: Profil Institute for Metabolic Research, Neuss, Germany .2005;5:38-41.
- 23- Jandeleit-Dahm, Karin AM; Tikellis, Christos,et,al; Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. Journal of Hypertension. 2005;23(3):463-473.
- 24-E. Torlone1, A. M.Rambotti1, G. Perriello et,al: ACE-inhibition increases hepatic and extrahepatic sensitivity to insulin in patients with Type 2 (noninsulin-dependent) diabetes mellitus and arterial hypertension; Diabetologia , 1991; 34(2):119 – 125.

تاثير تحت الجرع لـACE-I في تحسين التحسس للانسولين في مرضى داء السكر من النوع الثاني

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الخلاصة:

تم اختيار 30 مريض بالنوع الثاني من داء السكري الغير مسيطر عليه تتوسط اعمارهم بينَ (44.34 ±7.15) سَنَوات ومدّتهم مِنْ مرض السكَرِ كَانَت(8.48 ±8.27) سَنَوات،في مركز ابحاث ومعالجة السكري وتحت اشراف دكتور اختصاص،تم ابعاد مرضى ضغط الدم وامراض الكلى .تم قياس ضغط الدم ،مستوى الكلوكوز في الدم ،شرود الكلوكوز بعد الاكل، والالبومين يوريا قبل وبعد شهرين من العلاج يوميا بالكابتوبريل.اظهرت النتائج انخفاض معنوي (0.01) كبير في شرود الكلوكوز بعد الاكل، والالبومين يوريا قبل وبعد شهرين من العلاج يوميا بالكابتوبريل.اظهرت النتائج انخفاض معنوي (0.01) كبير في شرود الكلوكوز بعد الأكل في المجموعة التي تناولت مادة الكابتوبريل مع الكلبنكلمايد بالمقارنه مع ماقبل استخدام المابتوبريل عند حَسابَ منطقةِ تحت المنحنى. أظهرت هذه النتائج فعالية الكابتوبريل الأيجابية في زيادة حساسية انسجة الجسم لفعالية الأنسولين مما يؤدى الى تحسين السيطرة على مستوى الكلوكوز في الدم.