Evaluation of the effectiveness of candesartan, diltiazem, or their combination on normo-, micro- and macroalbuminuria in type 2 diabetic patients.

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ABSTRACT

***Background*: One third of diabetic patients ultimately develop nephropathy. Microalbuminuria (MIA) is an earliest sign for diabetic nephropathy and its measurement is mandatory for early prevention of end stage renal failure. Drugs which prevent development of MIA may delay deterioration of renal function.**

***Aim*: To evaluate effectiveness of candesartan, diltiazem or their combination on MIA in diabetic patients.**

***Methodology*: 104 diabetic patients attending outpatient clinic at local Basrah hospitals were recruited for the study, 64 patients had MIA, and 40 patients were normoalbuminuric. Each group was subdivided into three subgroups; each subgroup was treated with either candesartan 8 mg, diltiazem 90 mg, or their combination for six months. Albuminuria, FBS, HbA1c, serum creatinine, serum potassium, total cholesterol and blood pressure were measured after 3 and 6 months. Results: candesartan, diltiazem and the combination significantly reduced MIA at the end of 3 and 6 months treatment in comparison to baseline. Candesartan significantly reduced MIA from 175.8 ± 134 µg/ml at baseline to 76.7 ± 57.4 and 40.1 ± 32.5 after 3 and 6 months respectively. Diltiazem reduced MIA from 122.2 ± 102.8 µg/ml to 67.2 ± 52.6 and 51.0 ± 37.6 at the end of 3 and 6 months respectively. The combination reduced MIA from 174.6 ± 106.4 µg/ml to 93.2 ± 67.2 and 46.1 ± 53.0. In normoalbuminuric patients, the reduction with the three treatment modalities from baseline was small. The three treatments reduced blood pressure without causing hypotension.**

***Conclusions*: Candesartan, diltiazem, or the combination reduced albuminuria in diabetic patients with normo-, micro- or macroalbuminuria.**

تقييم فعالية الكانديسارتان، ديلتيازيم، أو كليهما على مستويات الألبومين ذات التركيز القليل، أو التركيز الطبيعي او التركيز العالي في الإدرار في مرضى السكري من النوع الثاني

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الخلاصة:ثلث مرضى السكري يتعرضون في نهاية المطاف الى اعتلال الكلية. ويعتبر الألبومين ذات التركيز القليل في الإدرار (Microalbuminuria) (MIA) من العلامات المبكرة لأعتلال الكلية السكري و قياسه إلزامي للوقاية المبكرة من الفشل الكلوي وان الأدوية التي تمنع ظهور الألبومين ذات التركيز القليل في الإدرار قد تؤخر تدهور وظيفة الكلى.

الهدف: لتقييم فعالية الكانديسارتان، ديلتيازيم، أو كليهما على (MIA) في الأدرار في مرضى السكري.

المنهجية: تم تجنيد ١٠٤ مريض مصاب بالسكري الذين حضروا العيادة الخارجية في المستشفيات المحلية في مدينة البصرة للدراسة، وكان ٦٤ مريضا لديهم (MIA)، و٤٠ مريضا لديهم تركيز معتدل للألبومين في الأدرار. وتم تقسيم كل مجموعة إلى ثلاث مجموعات فرعية؛ وعولجت كل مجموعة فرعية بالأدوية الأتية: 8 ملغم كانديسارتان، ٩٠ ملغم ديلتيازيم، أو الجمع بينهما لمدة ستة أشهر. وتم قياس البول الزلالي، نسبة السكر في الدم، نسبة HbA1c، الكرياتينين، والبوتاسيوم في مصل الدم، و الكوليسترول الكلي وضغط الدم بعد ٣ و ٦ أشهر من العلاج. النتائج : أدى استعمال الكانديسارتان ، ديلتيازيم والجمع بينهما إلى نقصان كبير يعتد به احصائيا في (MIA) في نهاية ٣ و ٦ أشهر من العلاج بالمقارنة مع المستويات قبل العلاج. وقد أدى استعمال كانديسارتان الى إنقاص (MIA) من ١٧٥.٨ ± ١٣٤ ميكروغرام / مل قبل العلاج إلى ٧٦.٧ ± ٥٧.٤ و ٤٠.١ ± ٣٢.٥ بعد ٣ و ٦ أشهر من العلاج على التوالي. وحدث انخفاض في (MIA) باستعمال الديلتيازيم من ١٢٢.٢ ± ١٠٢.٨ ميكروغرام/مل إلى ٦٧.٢ ± ٥٢.٦ و ٥١.٠ ± ٣٧.٦ في نهاية ٣ و ٦ أشهر على التوالي. وأدى استعمال العلاجين معا إلى انخفاض في (MIA) من ١٧٤.٦ ± ١٠٦.٤ ميكروغرام / مل إلى ٩٣.٢ ± ٦٧.٢ و ٤٦.١ ± ٥٣.٠. إما في المرضى الذين لديهم التركيز المعتدل للألبومين في الأدرار، فقد كان نقصان (MIA) في المجاميع الثلاثة قليلا. لقد ادى استعمال الأدوية إلى انخفاض في ضغط الدم ولكن لم يصل إلى درجة هبوط الضغط. الاستنتاجات: أدى استعمال كانديسارتان، ديلتيازيم، او الجمع بينهما الى نقصان الألبومين في مرضى السكري والذين لديهم البومين ذات التركيز القليل والطبيعي والمرتفع .

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INTRODUCTION

Diabetic nephropathy is the most common cause of end-stage renal disease.[1] Microalbuminuria represents the earliest clinical evidence of diabetic nephropathy.[2] The WHO has predicted a worldwide increase in the number of patients with diabetes from 100 million to 360 million in 2030[3] and between 20% and 40% of patients with diabetes mellitus ultimately develop nephropathy.[4] As the prevalence of diabetes is increasing, the prevalence of diabetic nephropathy is expected to rise as well. Thus diabetic nephropathy has become one of the most challenging health problems.[5] It is reported that deterioration in kidney function can be slowed down by preventing or decreasing the occurrence of microalbuminuria.[6] Among the widely studied groups of drugs with a documented anti-microalbuminuric effect in diabetes is angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers. These drugs were investigated at variable doses and variable study designs, in hypertensive and non hypertensive diabetic patients.[7-9] The conclusions derived from these studies, that these drugs reduced microalbuminuria to a variable degree and thus help in preventing deterioration in renal function independent to blood pressure lowering effects.[10-11] Candesartan reduced albuminuria in diabetic patients both with micro- and macroalbuminuria, but in diabetic patients with normal level of albuminuria, candesartan initially reduced albuminuria but on long term treatment this effect tends to disappear.[12] Diltiazem reduced albuminuria to a significant level and subsequently possesses renoprotective properties.[13] Both drugs are effective in the treatment of hypertension as monotherapy however, in high and uncontrolled hypertension in which more than one antihypertensive drugs is required, the combination of candesartan and diltiazem can be considered since both drugs are well tolerated and had no known adverse drug interactions between them. The aim of the study therefore was to investigate the effectiveness of monotherapy with candesartan, diltiazem as well as the combination of the two on microalbuminuria in diabetic patients.

PATIENTS AND METHODS

This study was an open, randomized controlled clinical trial, performed among consecutive patients with type 2 diabetic patients attending the outpatient clinic at Basrah General Hospital and a private clinic in Basrah during the period from November 2011 to October 2012. The study included diabetic patients of either gender with normo-, micro- or macroalbuminuria. The study protocol was approved by the College of Medicine Ethics Committee. The patient's age was between 25–75 years. Decision to include patients for the study was based on answering and filling a questionnaire form and meeting the inclusion criteria which, in addition to the specified age range, included diabetic patients with nephropathy with or without hypertension. Patients were excluded from the study if they had one or more of the following criteria: kidney disease of non-diabetic origin, fever, heart failure, urinary tract infection, prostatitis, menstruation, malignancy, pregnancy. Patients on any treatment apart from anti-diabetic drugs were excluded. The patients were first screened for the presence of albuminuria by examining an early morning urine sample. Two hundred and nine (209) patients were screened, 95 were men and 114 were women. One hundred and five patients were excluded, 83 patients were lost during follow-up; three women unexpectedly became pregnant during the study, and 19 patients due to severe illness. One hundred and four diabetic patients fulfilled the inclusion criteria and included in

the study. Sixty four patients had microalbuminuria, and referred to (microalbuminuria group) and 40 patients had normal albuminuria (normoalbuminuria group). Patients in the microalbuminuria group or normoalbuminuria group were randomly subdivided into three subgroups, group 1, group 2, and group 3. Patients in group 1 received candesartan 8 mg (Blopress. Hikma Pharmaceutical, Jordan), group 2 were treated with diltiazem 90 mg (Bi-Tildiem, Sanofi-Aventis, France) and group 3 were treated with the combination of candesartan 8 mg plus diltiazem 90 mg once daily. Microalbuminuria was measured by Eliza method using a special kit, (DRG Company, USA). For this test 20 ml of urine were collected in the early morning and stored at approximately 2-8 ◦C and assayed within 5 days after collection. Seven milliliters of blood was obtained by venipuncture for the following measurements: HbA1c (by Eliza kit set to a wave length of 450 nm), lipid profile (E6, Biolab, France for cholesterol kit and 0003, Human, Germany for triglyceride kit), Plasma glucose (measured spectrophotometrically using kit S591E, Plasmatec, UK), potassium level (spectrophotometric method), creatinine level (H54, Human, Germany), and blood urea by a standard method.

Statistical analysis

SPSS program version 15 was used for data analysis. Data were expressed as mean±SD. Student t-test for independent samples was used for comparison of means. P-value less than 0.05 was considered significant.

RESULTS

One hundred and four patients (104) with diabetes mellitus had completed the study. Patients characteristic are listed in Table-1.

Table 1. Patient characteristics

Parameters (Mean±SD)	**Microalbuminuria group (n=64)**	**Normoalbuminuria group (n=40)**
Age (years)	56.5 ± 10.4	47.7 ± 13.5
Gender (M/F)	22/42	11/29
Duration of diabetes mellitus (years)	11.8 ± 7.3	6.5 ± 3.0
Type of diabetes (%) Type 1 Type 2	 25 75	 23 **77**
Blood pressure (mmHg) Systolic blood pressure Diastolic blood pressure	 147.6 ± 21.5 89.4 ± 10.0	 140.9 ± 16.1 85.8 ± 8.0
Microalbuminuria (µg/ml)	155.2 ± 116.6	11.5 ± 5.6
Serum creatinine (mg/dl)	0.7 ± 0.2	0.7 ± 0.2
HbA1c (%)	8.5 ± 1.9	8.4 ± 1.8
Fasting blood glucose (mg/dl)	151.9 ± 55.2	150.8 ± 45.9

Candesartan significantly reduced microalbuminuria from 175.8±134 µg/ml at baseline levels to 76.7±57.4 µg/ml and to 40.1±32.5 µg/ml at the end of three and six months treatment respectively, P-value <0.001. Diltiazem had significantly reduced microalbuminuria from 122.2±102.8 µg/ml at the baseline to 67.2±52.6 µg/ml and to 51.0±37.6 µg/ml at the end of three months and six months treatment respectively. While patients receiving the combination, microalbuminuria was significantly reduced from a baseline value of 174.6±106.4 µg/ml to 93.2±67.2 µg/ml and to 46.1± 53.0 µg/ml at the end of three months and six months treatment respectively, P<0.001 and between the six and the three months values for the combination, P< 0.01 (Table-2).

***Table 2. The effect of candesartan, diltiazem or their combination on albuminuria in diabetic patients with micro- or macroalbuminuria*.**

Treatments	Microalbuminuria (µg/ml)			
	Baseline Mean ± SD	**At the end of three months Mean ± SD**	**At the end of six months Mean ± SD**	**Baseline corrected value for six months treatment**
Candesartan (n=22)	175.8 ± 134	76.7 ± 57.4‡	40.1 ± 32.5‡	-135.7 ± 116**
Diltiazem (n=24)	122.2 ± 102.8	67.2 ± 52.6‡	51.0 ± 37.6‡	-71.2 ± 70.9
Combination (n=18) candesartan /diltiazem	174.6 ± 106.4	93.2 ± 67.2‡	46.1 ± 53.0‡*	-128.4 ± 80.9**

‡ Significantly different from the corresponding baseline value, P< 0.001
*** Significantly different from the corresponding three months value, P< 0.01**
**** Significantly different from the corresponding value of diltiazem, P-value <0.05**

In diabetic patients who are normoalbuminuric, treatments for six months exhibited a small but significant reduction in albuminuria. The baseline value of albuminuria was 12.1±6.3 µg/ml before treatment with candesartan which was significantly reduced to 6.8±2.8 µg/ml at the end of three months treatment, and further reduced to 5.1±2.4 µg/ml at the end of six months treatment, P<0.01. The same pattern of effect was observed with diltiazem and the combination of candesartan and diltiazem (Table-3).

***Table 3. The effect of candesartan, diltiazem or their combination on albuminuria in normoalbuminuric diabetic patients*.**

Treatments	Microalbuminuria (µg/ml)			
	Baseline Mean ± SD	**At the end of three months** Mean ± SD	**At the end of six months Mean ± SD**	**Baseline corrected value for six months treatment**
Candesartan (n=16)	12.1 ± 6.3	6.8 ± 2.8	5.1 ± 2.4*†	-7.0 ± 4.6
Diltiazem (n=14)	9.9 ± 4.5	5.8 ± 1.9†	3.6 ± 1.6*†	-6.3 ± 4.4
Combination (n=10) candesartan /diltiazem	12.9 ± 5.6	5.1 ± 2.0†	2.9 ± 1.1*†	-10.0 ± 5.7

†Significantly different from baseline values, P< 0.01
*** Significantly different from three months values, P< 0.01**

Blood pressure was reduced by all treatments to a safe level and none of them had hypotension. Results for the effect of treatment on systolic and diastolic blood pressure are presented in (Table 4 and 5). None of the treatments adversely affect biochemical parameters. Drug interaction with the combination was not reported.

Table 4. The effect of candesartan, diltiazem or their combination on systolic blood pressure in micro- or maroalbuminuric diabetic patients.

Treatment	Systolic blood pressure (mmHg) Mean ± SD			
	Baseline	**After three months**	**After six months**	**Baseline corrected value for six months treatment**
Candesartan	149.9 ± 16.9	133± 10.8	126.1 ± 12.5**	-27 ± 25.5
Diltiazem	139.4 ± 14.6	131.2 ± 14.0	124.6 ± 15.7*	-14.2 ± 9.1
Combination	155.8 ± 29.9	147.5 ± 17.8	128.8 ± 14.2**	-28.3 ± 14.2¥

*** Significantly different from baseline, P-value< 0.05**

**** Significantly different from baseline, P-value< 0.01**

¥ Significantly different from the corresponding value of diltiazem, P-value < 0.01

Table 5. The effect of candesartan, diltiazem or their combination on diastolic blood pressure in micro- or maroalbuminuric diabetic patients.

Treatment	Diastolic blood pressure (mmHg) Mean ± SD			
	Baseline	**After three months**	**After six months**	**Baseline corrected value for six months treatment**
Candesartan	93.6 ± 9.6	82.6 ± 6.8	80 ± 40.26	-16.9±11.8
Diltiazem	85.6 ± 8.6	84.3 ± 8.6	76.2 ± 16.1	-9.6 ± 14.6
Combination	89.2 ± 10.6	82.9 ± 6.4	79.2 ± 5.1	-11.3 ± 9.1

DISCUSSION

As the incidence of diabetes is increasing worldwide, the prevalence of diabetic nephropathy is increasing.[14] Urinary albumin excretion (albuminuria) is a land mark of kidney damage; however, albuminuria which is defined as the presence of small amount of albumin in urine (less than 20ug/ml) is a valuable early indicator of kidney damage years before frank albumin is detected in urine. In the present study ELISA method is used for measurement of albuminuria. This method is one of the most sensitive methods available. It has the advantage of being simple, precise, sensitive, and easy to perform for quantitative determination of a broad range of 0.3 to1280 µg/ml of urinary albumin levels.[15-16] The present study was designed to investigate the effectiveness of candesartan, diltiazem or their combination on diabetic patients with normo-, micro- or macroalbuminuria in a small population in Basrah. It is worth mentioning that racial differences have an impact on the distribution of microalbuminuria among populations. The results of the present study revealed that candesartan at a dose 8 mg/day had significantly reduced albuminuria in diabetic patients with micro- or macroalbuminuria with a percent reduction in microalbuminuria of 74% using 8mg. This result is consistent with other published studies. One of these studies, 8mg, 16mg and 32mg candesartan significantly reduced microalbuminuria by 33% using 8mg, 59% by 16 mg and 53% by 32mg.[17] In another study,

in which 66 diabetic patients with microalbuminuria were studied. It was found that candesartan at a dose of 16 mg once daily is as effective as lisinopril 20 mg once daily in reducing microalbuminuria.[18] The percent reduction in microalbuminuria in this study is higher than values previously published in the white population from Europe and United States. It has been found that microalbuminuria is two or three folds higher in the black people with diabetes in comparison to the white.[19-20] However, the magnitude of reduction in microalbuminuria by antihypertensive drugs and the contribution of racial differences to that had not been sufficiently studied. The studied population in the present study is sufficiently different genetically and ethnically from the whites or the blacks and therefore, the contribution of racial differences to the observed marked effect on microalbuminuria cannot be ruled out. Doses of candesartan lower than doses used in the present study has been tried and found effective in lowering microalbuminuria. Low doses of candesartan have been studied in 127 type 2 diabetic patients with proteinuria. Candesartan at doses 2, 4, or 8 mg for 12 weeks has been found useful in reducing proteinuria in comparison to placebo.[21] The effect of candesartan, diltiazem or their combination on albuminuria in diabetic patients who had at the time of entry to the study, normal albumin levels in urine (normoalbuminuria) was evaluated. Candesartan in the present study significantly reduced albuminuria from 12.1 ± 6.3µg/ml at baseline to 5.1 ± 2.4µg/ml at the end of sixth month, $P < 0.01$. This result may suggest that future development of microalbuminuria in diabetic patients can be prevented by the use of candesartan. The result of the present study is, at least in part in agreement, with the results obtained in a placebo controlled study in which 5231 diabetics patients were treated with candesartan for 4.7 years.[12] In that study, in spite of the obvious effect on normoalbuminuria in the first six months treatment with candesartan which is consistent with our results, such effect disappeared as treatment continued. It can be speculated that the lowering effect of candesartan on albuminuria may unfortunately, disappear if the study is extended for a long period of time. The mechanism of renoprotection by candesartan may be complex. High glucose stimulates expression of renin and angiotensinogen in mesangial and tubular cells. This stimulation results in an increase in local angiotensin II concentrations which may, in turn, induce several cytokines and growth factors. Therefore blockade of the over expressed renin angiotensin aldosterone system may lead to renoprotection.[22] Candesartan, in addition has been shown to have vasodilator effects within the renal circulation by decreasing renal vascular resistance which leads to reduce leakage of albumin from capillaries to renal glomerulus.[23] The decision to include diltiazem in this study was made since it is relatively safe antihypertensive drug and frequently prescribed to diabetic patients without interfering with diabetic control. It has in addition, an additive antihypertensive effect when used in combination with candesartan when effective antihypertensive drugs are required in patients not well controlled by monotherapy. Diltiazem in the present study as in other published studies lower blood pressure to a safe level in addition to lowering microalbuminuria.[24] Diltiazem has been shown to have a beneficial effect on diabetic nephropathy, decreasing proteinuria and slowing progression of the disease.[25] In addition, diltiazem by decreasing intra glomerular pressure and dilating efferent arterioles [26] may lead to microalbuminuric lowering effect. Diltiazem has not been studied previously in normoalbuminuric diabetic patients. Our results revealed that

diltiazem 90 mg for six months reduced albuminuria significantly from 9.9±4.5µg/ml at the baseline to 5.8±1.9µg/ml and 3.6±1.6µg/ml after treatment at the end of three and six months respectively, however, we can not speculate if this reduction in albuminuria will continue beyond treatment for six months. The combination, candesartan and diltiazem, significantly reduced microalbuminuria in diabetic patients with micro- or macroalbuminuria and in patients with normoalbuminuria, although the magnitude of reduction is not significantly different from candesartan monotherapy but the reduction in systolic and diastolic blood pressure is additive and thus such combination may provide a reasonable therapeutic approach for diabetic patients with high blood pressure not well controlled by monotherapy particularly if microalbuminuria is detected. In conclusion candesartan reduced albuminuria in diabetic patients with normo-, micro- or macroalbuminuria, a result which was observed with the combination. Candesartan alone or combined with diltiazem reduced albminuria greater than diltiazem monotherapy. All the three treatments modalities reduced blood pressure independently to their effect on microalbuminuria.

Acknowledgement: The authors would like to thank Dr. Talib kames, Head of the Department of Internal Medicine at Al-Zubair General Hospital in Basrah, for his great help in recruiting and following up patients for the study.

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