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Comparative effect of lisinopril and lacidipine on urinary albumin 'excretion in patients with type 11 diabetic nephopathy

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Summary
This study was carried out to assess whether with a similar degree of blood pressure reduction, Lisinopril compares favorably or otherwise with lacidipine in respect of effects on urinary albumin excretion and renal function as assessed by creatinine clearance, plasma creatinine, urea and electrolytes.Thirty hypertensive diabetic nephropathy patients with moderate hypertension were studied. After a 2-week washout period, they were allocated into two groups matched at baseline for age, sex, weight, blood pressure, and urinary albumin excretion rate as well as creatinine clearance. There were 8 males and 7 females in each group. One group received lisinopril (with furosemide if needed to control BP) and the other group received lacidipine. Staged increases in doses of antihypertensives were used until BP was controlled or maximum dose of 40mg/day lisinopril or 8mg/day lacidipine was reached. Furosemide was added to lisinopril if BP was not controlled at 40mg/day. These medications were given for 12 weeks at the end of which measurements done at baseline were repeated. Comparison of baseline and end of study values of these parameters within the groups and between the two groups were made. Lisinopril group and lacidipine group achieved similar and highly significant reduction in blood pressure levels $P < 0.001$. There was reduction in urinary albumin excretion rate in both groups but this only reached statistical significance in the lisinopril group [480] [269] mg/day vs. 315 [202] mg/day $P < 0.05$] while for the lacidipine group it was not significant [491] [257] mg/day vs. 335 [182] mg/day $P > 0.05$]. However, comparison of albumin excretion rate between both groups at baseline and at end of the study did not show any significant difference, $P > 0.1$. With both drugs there is a tendency for creatinine clearance to increase and plasma creatinine to drop while plasma potassium tended to rise more with lisinopril than lacidipine but differences within and between both groups, did not reach statistical significance $P > 0.05$. In conclusion, blood pressure reduction was comparable in both drugs; both drugs reduced albuminuria but lisinopril appeared superior. Treatment with both drugs tended to increase creatinine clearance but both had no significant effects on blood sugar.

Keywords: *Comparative: effects: lisinopril: lacidipine: albuminuria: type 2 : diabetic: nephropathy*

Résumé
Cette etude a ete faite dans le but d'evaluer si avec un degree similaire de la reduction de la pression du sang, Lisinopril est favourable par rapport a Lacidopline sur les effets de l'ecretion de l'albumine dans l'urine et la foretion renale comme evaleur par la disparition de la creatinine, les creatinine du plasma, l'uree et les electrolytes. 30 patients diabetique avec la nephopatie et une hypertension moderee ont ete etudies. Apres deux semaines de lavage, ils etaient subdivises en deux groupes en fontion de l'age, sex, poids, pression arteielle du sang, le taux d'excretionde l'albumine par l'urine airisi que le degagement de la creatinine. If groupe etait traite au lisinopril (avec furosemide si possible pour controller la pression arterielle) et le second au lacidipine. Les doses des anti-hypertensifs augmentaient jusqui a ce que la PA etait controller ou un une doxe maximale de 40mg/jour de lisinopril ou 8mg/jour de lacidipine etait atteirite. La furosemide etait ajoutee a lisinopril si la PA n'etait pas contrilee a 40mg/jour. Ces medicaments etaient administers pendant 12 semaines a la fin desiquelle les measures etaient prise de facon repetee. La comparaison de la lique de base et les valeurs de le fin d'etude de ces parameters dans et entre les deux groupes etait effectuce. Les deux groups ont montre une reduction significative similoure et elevee de la PA, P<0, 001. La reduction du taux d'albumine dans le groupe traite au lisinopril (480 (269)mg/jour contre 315 (202) mg/jour P<0,05) alors que pour lacidipine, ceci n'etait pas significatif [491(257)mg/jour contre 335 (182)mg/jour, P>0,05}. Cependant, la couparaison du taux d'excretion de l'albumine entre les deux groups a la base et a la fin de l'etude n'a montre aucune difference significative entre les groupe. P>0,1. Avec les deux medicaments, il yavait une tendence de la disparition de la creatine d'augmenter et la creatine du plasma de diminuer alors que le plasma potassium tendait-a augmenter plus avec lisinopril que lacicidine, mais les differences dan et entre les deux groupe n'ont pas atteint le mivean statistique de la PA etait comparable dans les deux medicaments et ces dermier reduisaient l'albuminuria avec celui de lisinopril atteignant un niveau significatif. Les deux medicaments tendent a argmenter la creatinine mais n'eut aucum effet significaty sur la quantite du sucre dans le sand.

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Introduction

Diabetic patients are 17 times as prone to kidney disease as non-diabetic people[1]. Diabetic Nephropathy (DN) is a micro-vascular complicsation of diabetes mellitus and is defined clinically as the presence of persistent proteinuria >500mg/24h. Albuminuria > 300mg/24h in a diabetic patient with concomitant retinopathy and often elevated blood pressure but without urinary tract infection, other renal disease or heart failure [1,2,3]. DN is a major cause of morbidity and mortality in diabetic patients and is now the most common single cause of end stage renal disease (ESRD) in the western world [4]. There is also evidence that some racial groups including Blacks with DN may have a greater predisposition to ESRD than whites [5]. In Nigeria, DN ranks after chronic glomerulonephritis and hypertension as a cause of ESRD6. In diabetes, albuminuria is the clinical marker of DN1. Increasing level of albumin in urine is associated with progression of DN [7,8], while reduction in albuminuria predicts diminished progression in DN [8]. Elevated blood pressure (BP) levels are observed in diabetic. This association carries a significant increase in mortality and morbidity due to atherosclerosis and micro-vascular diabetic complications. This relationship between arterial blood pressure and DN is a complex one with DN increasing blood pressure and blood pressure accelerating the course of nephropathy. Anti-hypertensive drugs are capable of limiting the progressive decline in GFR to the extent that they could lower urinary protein excretion rate. Of the anti-hypertensive drugs, angiotensin converting enzyme (ACE) Inhibitors appear to be superior and have been shown in some

studies to decrease albuminuria and proffer protection of renal function independent of their action on systemic blood pressure. ACE inhibitors also have no adverse effects on blood glucose and lipids, a property which, is desirable in diabetics. However, they are not very effective as monotherapeutic agents in the treatment of hypertension in blacks in addition to their attendants side effects [9,10]. Although their antihypertensive action may be enhanced by addition of a diuretic, this may negate their salutary effects on blood glucose and lipids leading to increased cardiovascular mortality. On the other hand, calcium channel blockers (CCBs) are effective as monotherapy of hypertension in blacks and like ACE inhibitors do not adversely affect blood glucose and lipids, [11]. However CCBs are not known to have an innate ability to decrease albuminuria but may do this by reducing blood pressure. Some studies in diabetic patients have revealed same beneficial effects of calcium antagonist drugs and ACE inhibition on albuminuria and progression of DN [12]. This study was carried out to assess whether with a similar degree of blood pressure reduction, Lisinopril compares favorably or otherwise with lacidipine in respect of effects on urinary albumin excretion and renal function in an African population.

Subject and methods

This study was undertaken at the University College Hospital (UCH) Ibadan, and study subjects were all Nigerian patients with NIDDM attending the diabetic clinic at UCH. Diabetes Mellitus was diagnosed according to WHO Criteria.13 Classification of patients as type 2 diabetes mellitus was clinical and based on diagnosis of diabetes mellitus made after age of 40years and patient controlled using diet with or without oral hypoglycemic drugs [13]. In addition all subjects had hypertension, clinical diabetic nephropathy with dipstick positive albuminuria.

Ethical approval was sought and obtained from the hospital's research and ethics committee. Patients with type 2 diabetes mellitus, attending the diabetic and renal clinics of UCH, Ibadan, were recruited after an informed consent was obtained. Only those with known duration of diabetes >5 years were evaluated as albuminuria is said to be rare with disease duration of <5 years. Relevant clinical history and physical examinations were carried out. Patients were examined and features suggestive of secondary causes of hypertension were looked for. Fundoscopy after dilatation of the pupils with a mydriatic agent was done. Only patients with diabetic retinopathy (background or proliferative) were included. The patients had their urine tested with commercial dipstick test for albumin (Albustix - AMES) during three consecutive visits to the clinics, spaced one to two months apart. Those with at least, two positive urinalyses and without evidence of infection were sent for urine microscopy culture and sensitivity as well as for renal ultrasonography. Patients were included in the study if they had dipstick (albustix) positive urine on at least two occasions in previous six months, diabetic retinopathy on fundoscopy and normal renal ultrasound scan findings. Elevated blood pressure (BP) with systolic blood pressure (SBP) >140mmHg and diastolic BP (DBP) 90-114 mmHg and no evidence of urinary tract infection on urine microscopy culture and sensitivity. Patients were excluded from the study if plasma potassium was >5.0mmoi/L, plasma creatinine >2.0mg/di creatinine clearance <60mls/mm or there was urinary tract infection, presence of heart failure, history of myocardial infarction or angina, aortic outflow obstruction, cerebrovascular disease, severe hypertention (DBP>114mmHg), accelerated or malignant hypertension, clinically significant abnormality of liver, haemopoetic or endocrine system and malignancy as well as women who were likely to get pregnant. Those on antihypertensive drugs had the drugs discontinued for a two-week washout period before re-evaluation for inclusion in the study. Baseline characteristics of the subjects were recorded. Subject's age, gender, weight and height were noted. Baseline blood pressure, fasting blood sugar, plasma electrolytes, urea and creatinine, creatinine clearance and 24h urinary albumin were estimated at the beginning and at end of study. Age was recorded to the nearest whole year. Weight was measured with subjects in light clothing and without shoes on bean type balance scale calibrated with standard weights. Height was measured using an anthropometric planed with subject not putting on shoes or headgear. Body mass index (BMI) was calculated using the formula: BMI = Weight (kg)/[Height]2 (m2). Blood Pressure was measured using a mercury sphygmomanometer (Accosson, London).

The systolic (phase I) and the diastolic (phase V) pressures were rounded off (upwards) to the nearest 2 mmHg. This was repeated after 1-2 minutes and the two readings averaged. On the morning of completing the twenty-four hour urine collection, the subjects returned the collected urine and they were each questioned again to ascertain their compliance with the procedure. Urine samples were discarded when unsatisfactory explanations were given. Total volume of urine was measured using a large graduated cylinder and an aliquot was taken for analysis for creatinine and albumin after centrifuging. The aliquot was stored deep-frozen before analysis. Goal of anti-hypertensive therapy was to achieve a BP< 140/90 mmHg. Staged increases in the doses of antihypertensive agents were used Lacidipine was commenced at a daily dose of 4mg except for the elderly (aged>65 years) who were started on 2mg. Daily drug dose was reviewed and increased by 2mg during follow-up visits until target BP was attained or a maximum dose of 8mg Lacidipine was used. Lisinopril was started with a test dose of 5mg and patients instructed to report if postural dizziness occurred. However in the absence of such complaint, after a day patient was instructed to increase the daily dose to 10mg. If target blood pressure was still not achieved in subsequent 2 weekly follow-up visits dose of lisinopril was increased to 20mg/day and then 40mg/day. When even at the latter dose BP remained uncontrolled, furosemide (a diuretic) was added at a starting dose of 40mg/day to enhance anti-hypertensive efficacy.

All subjects were on with the dietary regimen prescribed at the hospitals dietetics department and which remained unchanged through the period of the study. They were also instructed to continue on their oral hypoglycaemic drugs. Each subject received the trial drugs for a period of twelve weeks at the end of which blood pressure, plasma electrolytes, urea and creatinine clearance and 24hr urinary albumin were estimated. Fasting venous blood glucose estimation was also done Mean arterial pressure was estimated as DBP + (SBP – DBP)/3 Urinary albumin estimation was done using Bromocresol Green Method in the absence of radio-immunoassay. Plasma electrolyte, urea and creatinine, as well as urinary creatinine estimation were by standard techniques. All chemical analyses were done in the routine Chemical Laboratory Department of UCH, Ibadan.

Statistical analysis

Data collected were coded and entered into the database of Epi-info version 6.04b programme on an IBM compatible microcomputer and analysed. Results were presented as means ±SD or as count percent of status or category. Within group changes from baseline to end of study were done using paired test. The paired t tests as well as correlation and multiple regression analysis were done using SPSS (Statistical Packages

for the Social Sciences) software package. Level of significance was set at $P<0.05$.

Results

Thirty-seven subjects were recruited but 30 of them (16 males, 14 females) completed the study. Four of the subjects were lost to follow-up, 2 developed severe hypertension during washout period, and one had urinary tract infection. There were 15 patients (8 males, 7 females) in each group of Lisinopril and Lacidipine. Mean (SD) ages for the groups were 58.7 [5.7] years and 58.5 (8.4) years for lisinopril and lacidipine groups respectively. Mean (SD) duration of diabetes was 11.4 [6.4] years and 10.9 [6.3] years respectively for lisinopril and lacidipine groups. Mean (SD) duration of hypertension was 10.8 [7.7] years and 8.6 [7.7] years for the lisinopril and lacidipine groups respectively. Mean (SD) weight and body mass index were 67.4 [10] kg and 24.7 [3.5] kg/m2 respectively for the lisinopril group. For the lacidipine group the values were respectively 70.4 [13.6] kg and 25.8 kg/m2. Inter-group comparison of all the above parameters showed that there were no significant differences between them (Table 1)

Table 1: Clinical characterisitics of patients at baseline for the two groups. Data are means (SD)

	Lisino pril group	Lacidi pine group	P-value
Number of men	8	8	
Number of women	7	7	
Age (Years)	58.7(5.7)	58.5(8.4)	0.967
Duration of diabetes (yrs)	11.4(6.4)	10.9(6.3)	0.851
Duration of hypertension (years)	10.8(7.7	8.7(7.7)	0.297
Weight	67.4(10)	70.4(13.6)	0.619
Body mass index (kg/m2)	24.7(3.5	25.8(4.8)	0.604

Table 2 shows the laboratory data with inter/intra group comparison of both groups of patients at baseline and at the end of study. Mean (SD) albuminuria were 479.9 [269.0] mg/24h and 491.8 [257] mg/24h for lisinopril and lacidipine groups respectively. The mean (SD) blood pressure readings were in the mild to moderate range in both groups; mean (SD) creatinine clearance were 70 [14], and 71 [13] for Lisinopril and Lacidipine groups respectively. Mean (SD) plasma creatinine and electrolytes were also essentially normal for both groups. Mean (SD) fasting venous blood glucose was 105 mg/dl for lisinopril and 86 [28] mg/dl for the lacidipine group. Comparison of all laboratory values between the two groups did not show any significant differences (P>0.05). Mean (SD) 24h urinary albumin excretion values were 315 [202] mg and 355 [182] mg for lisinopril and lacidipine groups respectively at the end of study. Inter-group comparison of these laboratory parameters showed no significant differences between the groups (P>0.05).

In the Lisinopril group, the mean arterial blood pressure at baseline versus end of study were respectively 116 [6] mmHg vs 102 [6] mmHg ($p < 0.01$) This showed a very significant drop. Similarly, differences between baseline and end of study values of SBP and DBP were statistically significant $P < 0.01$. The difference in mean (SD) albumin excretion rate atbaseline, 480 [269] mg/24h versus value at end of study 315 [202] mg/24h was statistically significant $P< 0.05$. Also in the Lacidipine group, mean (SD) values were at baseline vs end of study for MAP 121 [9] mmHg vs 107 [15] mmHg; SBP 166 [18] mmHg vs 149 [21] mmHg and DBP 98 [9] mmHg vs 86 [14] mmHg respectively. These drops in MAP, SBP and DBP were very significant with p value < 0.01. Mean (SD) 24h urinary albumin excretion was 4911.8 [257] mg at baseline vs 335 [182] mg at end of study P= 0.051. This reduction in albuminuria did not reach statistical significance at 95% confidence level. Mean (SD) creatinine clearance rose from 71 [3] ml/min at baseline to 77 [16] ml/min at end of study, P = 0.231 which is no significant. Other values expressed as means (SD) at baseline vs end of study are as follows respectively: plasma creatinine 1.29 [0.25] mg/dl vs 1.2 [0.22] mg/dl; plasma urea 31.7 [12.2] mg/dl vs 33 [10] mg/dl; plasma potassium 4.38 [0.35] mmol/L vs 4.5 [0.7] mmol/L; plasma sodium 132 [7] mmol/L vs 130 [9] mmol/L; plasma chloride 100 [2] mmol/L vs 98 [5] mmol/L; plasma bicarbonate 23 [3] mol/L vs 23.3 [2.3] mmol/L and fasting venous blood glucose 86 [28] mg/dl vs 95 [56] mg/dl. The changes in these plasma electrolytes, urea and creatinine as well as fasting venous blood glucose were not statistically significant P > 0.1. Five subjects in the Lisinopril group had additional furosemide, 3 of them had 40mg/day while 2 had 80mg/day. Analysis of this group showed that furosemide did not affect any of the parameters measured above.

Table 2: Intra/intergroup comparison: Lisinopril and lacidi pine baseline values versus end of study values of clinic and biochemical data.

	Lisinopril Wk 0	Wk12	P value (two tailed)	Wk0	Wk 12	Lacidipine P value (two tailed)
Systolic blood pressure (mmHg)	160 (12)	142 (14)	0.000	166 (18)	149 (21)	0.001
Diastolic blood pressure (mmHg)	93 (4)	83 (4)	0.000	98 (9)	86 (14)	0.001
Mean arterial blood pressure (mmHg)	116 (6)	102 (6)	0.000	121 (9)	107 (15)	0.0002
24th Urinary albumin excretion (mg/24th)	479.9 (269.1)	315 (202)	0.021	491.8 (257)	355 (182)	0.051
Creatinine clearance (ml/min)	70 (14)	73 (14)	0.213	71 (13)	77 (16)	0.231
Plasma creatinine (mg/dl)	1.30 (0.23)	1.27 (023)	0.589	1.29 (0.25)	1.2 (0.22)	0.206
Plasma urea (mg/dl)	32.4 (8)	35 (9)	0.598	31.7 (12.2)	33 (10)	0.644
Plasma potassium (mmol/L)	4.39 (0.52)	4.7 (0.4)	0.077	4.38 (0.35)	4.5 (0.7)	0.650
Plasma sodium (mmol/L)	129 (7)	130 (6)	0.902	132 (7)	130 (9)	0.410
Plasma Chloride (mmol/L)	97 (5)	97 (5)	0.972	100 (2)	98 (5)	0.229
Plasma Bicarbonate (mmol/L)	23 (2)	22.8 (2.4)	0.847	23 (3)	23.3 (2.3)	0.903
Fasting blood glucose (mg/dl)	105 (47)	102 (42)	0.725	86 (28)	95 (56)	0.499

To determine variables correlating with albumin excretion in this study, correlation analysis were done to determine what variables correlated with baseline and end of study urinary albumin excretion. Blood pressures (SP, DBP and MAP), drug, age, sex, duration of diabetes, duration of hypertension, baseline creatinine clearance did not significantly correlate with baseline or end of study urinary albumin excretion. Also variables correlating with change in albumin excretion rate were assessed. None of the above parameters correlated significantly.

The following side effects were noted in the Lisinopril group in this frequency, dizziness 2, pedal edema 2, itching skin 7, dry cough 2, headaches 12 and impotence 5. In the Lacidipine group it was dizziness 2, pedal edema 3, itching skin 5, dry cough 1, headaches 8 and impotence 3.The differences in the frequencies of these side effects were not statistically significant P>1.0

Discussion

In this prospective non-randomised open parallel study, patients had to have diabetic retinopathy which increased the likelihood that the albuminuria these patients had was due to DN and not other glomerulopathies which may be prevalent in the non insulin dependent diabetic population [14]. Inclusion creteria of a minimum duration of diabetes of five years was decided upon to help minimize waste of scarce resources and focus on a subgroup of patients that would likely yield more of the desired subjects. It additionally also served to exclude some whose albuminuria may be of non-diabetic origin. It is appreciated that some genuine DN patients may have been excluded with use of these criteria since in NIDDM, DN may be present at time of diagnosis because of the long sub-clinical phase of the disease in some patients [1].

This study revealed comparable end of study values for the two groups in respect of the following: albuminuria, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, creatinine clearance, plasma creatinine, urea, electrolytes and fasting blood glucose. However, during intra-group comparison, the level of change in albuminuria from baseline to end of the study only reached statistical significance (95% level of confidence) in the lisinopril group. O' Donnell et al [15] in their study lasting [16] weeks found that in the lisinopril group albuminuria tended to decrease from 738.7 to 664 ug/min, but this did not reach statistical significance while in nifedipine group there was a tendency for a rise from 981.2 ug/min to 1072/5 ug/min (p = NS). Ferder, et al 16 found after a 12-month study that enalapril significantly reduced albuminuria while nifedipine had no effect on albumin excretion.

Concerning blood pressure control, both drugs showed similar and highly significant drop in SBP, DBP and MAP. This is similar to the findings of all previous studies mentioned [15,16], [18]. The creatinine clearance of both study groups did not significantly change from baseline confirming that reduction in albuminuria might not be due to reduction in creatinine clearance although this is in contrast with the results of other studies [15] , which showed deterioration of GFR in both lisinopril and nifedipine treated groups as well as enalapril and nifedipine treated groups respectively. Just as in this study, Romero et al [17] found no significant differences in the effects of the two classes of drugs on plasma potassium and sodium concentrations.

Dietary protein is one of the factors that affect urinary protein excretion. In some such similar studies protein intake was standardized for patients weight to ensure similar level of protein consumption, however because of lack of logistic facilities, this could not be done here. But it is believed that our local diets generally are of low protein content. These patients were all on traditional meals with quantities as specified by dieticians to meet each patient's management goal of glycaemic, blood pressure and weight control. All the patients were on local diet and claimed compliance with dietary instructions.

Sodium intake is known to affect the antihypertensive efficacy of ACE inhibitors and thus their effects on albumin excretion [16, 19]. None of the patients admitted being in the habit of addition salt to meals on the table after cooking. Furthermore, the use of furosemide (a diuretic) in some patients helped to excrete any excess salt and achieve sensitivity to the antihypertensive effects of ACE inhibitors.

Use of furosemide (a diuretic) as anti-hypertensive adjunct to lisinopril was based on the fact of poor efficacy of ACE inhibitors as monotherapy of hypertension in black race particularly in the diabetic population who are usually of low renin status 20. Without its use adequate blood pressure control may not have been achieved in some subjects. Furthermore previous studies [17,18] employed similar steps. There was concern about a possible confounding effect of use of furosemide on the principal measure of comparison i.e. albuminuria but intra-group analysis did not show any significant difference in albumin excretion rate and creatinine clearance due to the use of furosemide as in previous studies. We are therefore of the opinion that it did not significantly alter our findings in that respect.

Although Lisinopril appeared superior to Lacidipine in reducing albumin, the duration of this study of twelve weeks is no doubt rather short and may partly explain difficulties in demonstrating clear-cut differences in the two study groups. Limitation of resources is largely responsible for the chosen duration. It is noteworthy that the study by Corradi *et al* [18] suggest that the anti-albuminuric effect of nitredipine (a CCB) is evident only after a year. Therefore there may not have been enough time in this study for the full effects of the two drugs to be determined. A long-term assessment of both drugs may be required for firm conclusions to be made.

On the mechanism of relationship between albumin excretion rate and change in BP, it is thought that arterial blood pressure is one of the determinants of intraglomerular pressure and hence influences the magnitude of the albumin leak through an already porous glomerular membrane. Surprisingly this is not supported in this study and Romero *et al* [17] have obtained similar results in the studies. Other studies regarding correlation have employed logarithmic transformed change in albumin excretion rate as the dependent variable and not just absolute changes in albumin excretion rate.

The spectrum of side effects documented in the two drugs was similar, some of which were well known with both drugs. Both drugs did not appear to be superior to each other in terms of frequency of side effects noted in the study.

In conclusion, blood pressure reduction was comparable in both drugs. Although, the number of subjects studied was small, both drugs reduced albuminuria with that of Lisinopril reaching significance. Treatment with both drugs tended to increase creatinine clearance but both had no effects on blood sugar.

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