

Long-Term Electrolyte Effects during Initiation of Antihypertensive Therapy with Amlodipine or Hydrochlorothiazide in Diabetic Nigerians

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Abstract Information is scarce regarding the effects of amlodipine or hydrochlorothiazide therapy on serum and urine electrolyte profiles in hypertensive Nigerians with type 2 diabetes mellitus. Therefore, to evaluate whether amlodipine or hydrochlorothiazide would be preferable to initiate treatment, we randomized 40 newly diagnosed hypertensive subjects with controlled type 2 diabetes mellitus aged 43-68 years to amlodipine and hydrochlorothiazide treatment groups of 20 patients each (10 males, 10 females), and they were treated respectively, with amlodipine 10mg and hydrochlorothiazide 25mg, both drugs being given once daily for 48 weeks. Body mass index, blood pressure, 24h urine volume, serum and urine electrolytes were assessed at baseline and at the end of weeks 1, 3, 6, 12, 24, 36 and 48. The two drugs significantly reduced blood pressure, though the effect of amlodipine was significantly greater compared with that of hydrochlorothiazide ($P < 0.01$). Diuresis was significant in hydrochlorothiazide group ($P < 0.01$). Observed male/female serum Na^+ loss was $9.18 \pm 2.32/10.90 \pm 2.50$ and $13.30 \pm 1.34/15.10 \pm 1.77$ mmol/L for amlodipine and hydrochlorothiazide subgroups, respectively. There was a parallel significant ($P < 0.05$) natriuresis. Significant ($P < 0.05$) hypokalemia occurred in hydrochlorothiazide subgroups and overall male/female serum K^+ loss was $0.10/0.08$ and $0.16/0.24$ mmol/L for amlodipine and hydrochlorothiazide, respectively. However, there was no significant parallel kaliuresis. Significant ($P < 0.05$) disproportionate hypochloremia occurred in all subgroups, so also was the parallel chloriuria. By providing effective blood pressure control and beneficial biochemical effects, amlodipine therapy appears suitable for treatment of hypertension in these diabetic patients. Similarly, low dose hydrochlorothiazide therapy, which seems to have more marked effects in females, appears to have moderate biochemical complications in these patients and is, therefore, a logical alternative to substitute for or add to amlodipine therapy.

Keywords: Amlodipine, hydrochlorothiazide, electrolyte effects, hypertension, type 2 diabetes mellitus, Nigerians

1. Introduction

The prevalence of hypertension in patients with type 2 diabetes mellitus (DM) is at least twice that of non-diabetic individuals, with more than 75% of patients with DM having hypertension [1]. Controlling blood pressure (BP) to current treatment guideline goal of $< 130/80$ mmHg is of prime importance in patients with hypertension and DM because improved BP control has been demonstrated to substantially reduce cardiovascular as well as renal morbidity and mortality in these patients [2,3]. Although the importance of BP lowering in these patients is beyond doubt, recent findings [4,5], have questioned the value of aggressive BP reduction targets in these patients.

Treatment of hypertension in diabetic patients has been difficult in that medication adverse effects, including

biochemical and metabolic complications, are common [6]. For example, diuretics such as hydrochlorothiazide (HCZ) may significantly interfere with electrolyte or glucose homeostasis [7,8] whereas calcium channel blockers (CCBs) such as amlodipine (AML) though not associated with electrolyte imbalance may sometimes interfere with glucose metabolism during long-term use [9,10]. Although current treatment guidelines [2,11] recommend initial therapy with either an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in patients with concomitant hypertension and DM, these agents are less effective in hypertensive blacks compared to whites when used as monotherapy unless combined with diuretics or CCBs [2,12,13]. Consequently, diuretics or CCBs, which specifically address the low-renin, sodium (salt)-sensitive and volume-dependent hypertension prevalent in diabetics and blacks, have been suggested as obvious first choice agents [2,13,14,15].

However, even though AML and HCZ are frequently used to treat diabetics and non-diabetics in Nigeria, studies are scarce that have examined the effects of initiating antihypertensive therapy with AML or HCZ on serum and urine electrolytes in hypertensive diabetic Nigerians. Majority of studies in blacks regarding the effects of antihypertensive drugs in the context of hypertension and DM, have been done in Africans in diaspora but not in native blacks born and living in Africa. Furthermore, safety concerns have been raised about the use of thiazides in diabetic hypertensive patients [16,17] because of the worrisome high morbidity and mortality still associated with type 2 diabetes in Nigeria [17,18,19].

For the foregoing reasons and based on our earlier observations [20,21], we studied the long-term effects of initiating therapy with AML or HCZ in hypertensive Nigerians with type 2 DM. This report, therefore, supplements data which have appeared in studies cited above.

2. Materials and Methods

2.1. Population

Forty type 2 diabetic Nigerians of both gender with newly diagnosed essential hypertension (stages 1, stages 2) aged 43-68 years who were attending Central Hospital and Osigbemhe Hospital both in Auchi in Edo State of Nigeria were recruited into a randomized, open-label, prospective, two-center, out-patient, 48-week study between March 2008 and March 2009. The sample size was estimated based on the number of Nigerians that are believed to have hypertension with concomitant type 2 DM [22]; and to detect a difference of 1 unit in mean change in the measured variables, between both treatment arms with a power equal to 90% using a one sample t-test at a one-sided significance level of 0.05, this requires 20 patients per group.

Eligible participants had qualifying hypertension of blood pressure (BP) $> 160/90$ and $\leq 180/120$ mmHg measured on at least 2 occasions in lying/supine, sitting and standing positions using standardized methods [23]. Excluded were patients with identifiable cause of the hypertension except type 2 DM, clinical evidence of cerebrovascular, cardiac, renal, hepatic, gastrointestinal or endocrinologic disease except type 2 DM, hypersensitivity to AML and HCZ or related drugs, history of smoking, alcohol intake, substance abuse or mental illness. Also excluded were patients needing any concomitant medication (apart from oral antidiabetic drugs) e.g. digitalis, non-steroidal anti-inflammatory drugs, psychotropic drugs, monoamine oxidase inhibitors or oral contraceptives, that may interact with the trial drugs and pregnant or lactating females.

Controls comprised the parallel age and sex-matched hypertensives on HCZ. The research protocol was reviewed and approved by the Ethics Committees of Irrua Specialist Teaching Hospital Irrua, Nigeria (Ambrose Alli University College of Medicine Teaching Hospital) and Central Hospital Auchi, Nigeria. After suitable explanation of the study protocol in lay language, all literate patients gave informed written consent and the

illiterates thumb-printed the consent form before the beginning of the study.

2.2. Study Design

Subjects were examined by a standardized, pre-tested questionnaire seeking information on demographic data, the history of hypertension, DM, current drugs if any, educational and social status, dietary habits, smoking and alcohol intake, etc. The 40 patients were randomized to AML and HCZ groups each comprising 20 patients (10 males (M) +10 females (F)) using computer program-generated random numbers. Diabetes was treated in 32 patients with glibenclamide 5mg once daily and metformin 500mg once or twice daily as well as in 8 patients with gliclazide 80mg once or twice daily. Patients were instructed to take their drugs between 8 am and 10 am daily.

2.3. Measurements of Heights (m) Weights (wt) (kg) and BP (mmHg)

A stadiometer scale (Seca model, UK) was used for measuring height, with no shoes on; and a beam balance (Hackman, UK) was used to measure wt while in light clothing. Body mass index (BMI) was computed as wt divided by height squared. Systolic BP (SBP) and diastolic BP (DBP) were measured with a standard mercury sphygmomanometer (Riester Diplomat Presameter, Germany) using standardized methods [23] at the sitting, standing and supine positions; always between 8am and 10am. All constricting clothing on the upper arm were removed before any measurement and subjects were discouraged from talking or moving during measurements. The first phase of the Korotkov sound was regarded as the SBP while the fifth phase was regarded as the DBP. During measurement, readings were taken two consecutive times with an interval of at least one minute and the average recorded. During the study, subjects were not told the results of BP measurement.

2.4. Antihypertensive Intervention

Patients in AML group were treated initially with AML 5mg and the dose was doubled after 6 weeks if BP was not controlled while in HCZ group patients were treated with HCZ 25mg, both medications being administered once daily. The outpatient treatment lasted 48 weeks. The patients were monitored closely and outcome measures evaluated at baseline, before treatment and at the end of weeks 1, 3, 6, 12, 24, 36 and 48. Unequivocal patient identification was possible via a patient identification list consisting of the patient number, first name and surname.

The study medications AML and HCZ are licensed for long-term treatment of hypertension so dangerous side effects due to the medicaments were not to be expected. AML 5mg and 10mg tablets (Amlovar^R) were donated by Neimeth International Pharmaceuticals Ikeja, Nigeria: NAFDAC Reg No A4-0333; Manufacturing Date 07-2007 and Expiry Date 07-2010. HCZ 25mg tablets (Esidrex^R) were donated by Novartis Pharma SAS Nigerian Representative, NAFDAC Reg No OL-3705, Manufacturing Date 08-2007 and Expiry Date 08-2010.

2.5. Course of Study and Methods for Recording Efficacy and Safety

All patients were advised to maintain their usual diet (weight-maintaining no-salt-added diet) and regular physical activity but to avoid undue stress throughout the duration of the study. They were instructed to take their drugs every morning. Each patient was observed for about 2 hours after taking medication drug for the first time. Adherence in respect of intake of medication was encouraged by interviewing patients through phone calls, sporadic visits and pill counts outside the view of patients. To preclude white-coat effect, observer bias and to accurately assess the efficacy of the drugs, patients were followed up repeatedly at weeks 1, 3, 6, 12, 24, 36, and 48. At each visit, volunteered or spontaneous report of adverse events were assessed for severity and association with treatment; and the attending physicians/investigators also recorded any adverse events they observed themselves or elicited from the patient through careful interrogation like "How do you feel?" Adverse effects were mild and no patient withdrew from the study because of adverse events.

Response to therapy was defined as a decrease in the mean trough sitting SBP and DBP of 10mmHg or a drop to < 90mmHg with reduction of > 5mmHg. BP was regarded as controlled if the DBP was < 80mmHg and SBP < 130 mmHg. The effects of treatment on the various variables (except height) were assessed by comparing the values at each visit with the pretreatment baseline values.

2.6. Collection of Samples and Analysis

2.6.1. Urine

Each subject collected a 24h urine sample into a plastic container from Sunday 7 am to Monday 7 am at baseline (week 0) before treatment and on the evaluation days. The need to carefully collect all urine passed was well emphasized. The volume of 24h urine was measured with

a measuring cylinder and recorded on each evaluation day as well as urine Na⁺, K⁺ and Cl⁻ which were measured with an ion-selective electrolyte analyser branded Biolyte 2000 (BioCare Corporation, Hsinchu 300, Taiwan).

2.6.2. Blood

At baseline and at the end of weeks 1, 3, 6, 12, 24, 36, and 48, 10ml of venous blood was obtained from every patient by peripheral venepuncture into a plain sterile bottle. From the prepared serum sample of each subject serum Na⁺, K⁺ and Cl⁻ were assayed using ion-selective electrolyte analyser.

2.7. Statistical Analysis

All data are presented as mean \pm SEM or mean \pm SD (for age, height and weight) using the Proc ANOVA of SAS (2004). Where significant differences were noticed, mean separation was carried out using Duncan Multiple Range Test. Correlation between two sets of variables was determined using Spearman's rank correlation. $P < 0.05$ was regarded as significant.

3. Results

Table 1 shows that demographic and clinical characteristics in the 4 randomized treatment subgroups were comparable. The effects of treatment drugs on SBP and DBP in the trial subjects were significant. The duration of treatment effect on the variables was significant ($P < 0.0001$) and AML significantly reduced SBP and DBP more than HCZ ($P < 0.01$). Overall, the mean M/F SBP/DBP decrease from baseline was 27.0/17.5 vs 29.5/20.0mmHg for AML group and 23.5/17.5 vs 22.0/16.5mmHg for HCZ group, respectively. Those patients who achieved the goal BP of < 130/80mmHg were only 6 in AML group and 4 in HCZ group. Diuresis was significant ($P < 0.05$) in M and F HCZ subgroups at week 3.

Table 1. Demographic Characteristics and Baseline Blood Pressures of Hypertensive Diabetic Subjects (N = 20 [10M + 10F] per group)

Group	Characteristics	Male		Female	
		Range	Mean \pm SD/SEM*	Range	Mean \pm SD/SEM*
AML	Age(yrs)	46-61	53.90 \pm 5.04	45-62	53.10 \pm 5.38
	Height(m)	1.59-1.73	1.66 \pm 0.04	1.58-1.71	1.64 \pm 0.05
	Weight(kg)	74-90	83.20 \pm 5.13	72-89	80.0 \pm 4.71
	BMI.(kg/m ²)	29.37-30.10	30.25 \pm 0.24	28.92-30.48	29.00 \pm 0.70
	SBP(mmHg)	150-180	164.50 \pm 3.76*	155-180	166.50 \pm 2.24*
	DBP(mmHg)	100-115	104.50 \pm 1.89*	100-110	105.00 \pm 1.57*
HCZ	Age(yrs)	45-65	52.40 \pm 6.75	43-68	54.50 \pm 7.73
	Height(m)	1.62-1.74	1.68 \pm 0.04	1.58-1.70	1.64 \pm 0.03
	Weight(kg)	77-90	84.51 \pm 4.32	63-86	76.44 \pm 6.54
	BMI(kg/m ²)	29.39-30.00	29.96 \pm 0.19	26.30-29.76	27.50 \pm 0.53
	SBP(mmHg)	160-180	162.50 \pm 3.71*	150-180	162.00 \pm 2.62*
	DBP(mmHg)	90-115	104.50 \pm 1.89*	100-115	102.50 \pm 2.71*

Demographic characteristics and blood pressures are comparable in AML and HCZ groups; AML, Amlodipine; HCZ, Hydrochlorothiazide; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; M, male; F, female;

*, Standard error of mean

The effects of treatment drugs on serum Na⁺ (SNa⁺) are presented in Table 2. Significant (P < 0.0001) hyponatremic changes were noticed in all subgroups but the effect of HCZ was significantly (P < 0.01) greater than that of AML. Gender effect was significant (P < 0.01) for

response to treatment was more marked in F. The M/F% Na⁺ loss at week 48 was 9.18/10.90mmol/L (6.0/7.1%) for AML subgroups and 13.30/15.10mmol/L (8.7/10.1%) for HCZ subgroups. There was significant (P < 0.05) parallel natriuresis (Table 3).

Table 2. Effects of Monotherapy with AML and HCZ on Serum Na⁺ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	153.20 ± 2.33	151.50 ± 1.52	154.10 ± 4.89	149.90 ± 2.13	0.028*
1	152.10 ± 2.10	148.70 ± 1.17	152.70 ± 1.59	147.70 ± 1.84	
3	150.30 ± 2.07	147.80 ± 1.70	150.70 ± 1.52	145.90 ± 1.85	
6	147.70 ± 2.03	145.00 ± 1.31 _A	148.50 ± 1.44 ^a _A	143.10 ± 1.64 ^b _A	
12	145.70 ± 1.97 _A	143.70 ± 1.25 _A	144.70 ± 1.03 _{BA}	142.00 ± 1.68 _A	
24	145.02 ± 1.75 _A	142.60 ± 1.26 _A	143.80 ± 1.07 _{BA}	141.10 ± 1.57 _A	
36	144.18 ± 1.86 _A	142.50 ± 1.16 _A	143.70 ± 1.02 _{BA}	140.90 ± 1.47 _A	
48	144.02 ± 2.32 _A	138.20 ± 1.15 _A	143.20 ± 0.87 _B	134.80 ± 1.41 _B	

Significant differences within columns are indicated by AB and within rows by ab (P < 0.05); There are significant time-dependent hyponatremic changes in both groups; * (P < 0.01); other abbreviations are as used in Table 1; (N = 10 per subgroup)

Table 3. Effects of Monotherapy with AML and HCZ on Urine Na⁺ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	253.20 ± 2.33	251.50 ± 1.52	278.40 ± 6.26 ^a	265.70 ± 5.03 ^b	0.015*
1	260.10 ± 2.10	268.70 ± 1.17	281.30 ± 1.90	288.30 ± 5.09	
3	262.30 ± 2.07 _A	266.80 ± 1.70	286.50 ± 2.31 _A	283.80 ± 5.01 _A	
6	257.70 ± 2.03	262.00 ± 1.31 _A	284.70 ± 1.76 _A	281.80 ± 4.38 _A	
12	255.70 ± 1.97	260.40 ± 1.25 _A	287.70 ± 1.92 ^a _A	278.10 ± 4.74 ^b	
24	254.00 ± 1.75	256.60 ± 1.26 _A	281.10 ± 1.82 _A	274.10 ± 4.58	
36	253.90 ± 1.86	255.04 ± 1.16 _A	282.10 ± 1.90 ^a	273.70 ± 4.52 ^b	
48	254.06 ± 2.32	255.70 ± 1.15 _A	281.90 ± 1.85	275.00 ± 4.61	

Significant differences within columns are indicated by AA and within rows by ab (P < 0.05); Significant treatment effects and time-dependent natriuresis are demonstrated; * P < 0.01; other abbreviations are as used in Table 1; (N = 10 per subgroup)

Displayed in Table 4 are the effects of treatment on serum K⁺ (SK⁺). Only HCZ caused a significant K⁺ loss which was observed from week 24 and the effect was more marked in F (P < 0.01). Mean M/F SK⁺ loss at week 48 was 0.10/0.08mmol/L (2.47/2.00%) and 0.16/0.24mmol/L (3.42/5.74%) for AML and HCZ

subgroups, respectively. However, there was no significant parallel kaliuresis (Table 5). Table 6 shows significant (P < 0.05) disproportionate hypochloremia in all groups and the gender effect was insignificant. There was a corresponding hyperchloriuria which tended to normalize to baseline values after 24 weeks (Table 7).

Table 4. Effects of Monotherapy with AML and HCZ on Serum K⁺ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	4.05 ± 0.06	4.08 ± 0.08	4.05 ± 0.13	4.18 ± 0.07	0.039*
1	4.05 ± 0.06	4.04 ± 0.08	4.04 ± 0.04	4.16 ± 0.08	
3	4.05 ± 0.06	3.99 ± 0.08	4.03 ± 0.04	4.10 ± 0.07	
6	3.96 ± 0.06	3.96 ± 0.08	4.03 ± 0.04	4.08 ± 0.07	
12	3.97 ± 0.06	3.95 ± 0.08	4.01 ± 0.04	4.08 ± 0.07	
24	3.95 ± 0.06	3.93 ± 0.08 _A	3.98 ± 0.04	4.06 ± 0.08	
36	3.95 ± 0.06	3.93 ± 0.08 _A	3.96 ± 0.04 ^b	4.01 ± 0.07 ^a _A	
48	3.95 ± 0.06	3.92 ± 0.08 _A	3.96 ± 0.04	3.94 ± 0.07 _A	

Significant differences within columns are indicated by AA and within rows by ab (P < 0.05); Changes in serum K⁺ are significant in HCZ subgroups and gender effect is significant; * P < 0.05; other abbreviations are as used in Table 1; (N = 10 per subgroup)

Table 5. Effects of Monotherapy with AML and HCZ on Urine K⁺ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	80.20 ± 2.51	81.20 ± 2.07	83.20 ± 3.52	78.00 ± 2.35	0.572 ^{NS}
1	81.30 ± 1.88	81.70 ± 2.07	83.20 ± 1.11	78.00 ± 2.42	
3	81.40 ± 1.86	82.50 ± 2.09	83.90 ± 1.08	78.00 ± 2.35	
6	82.20 ± 1.92	81.40 ± 2.06	84.50 ± 1.76 ^a	78.00 ± 2.27 ^b	
12	82.20 ± 1.92	81.30 ± 2.01	84.60 ± 1.14 ^a	78.00 ± 2.35 ^b	
24	82.20 ± 1.92	81.20 ± 2.07	84.40 ± 1.07 ^a	78.00 ± 2.07 ^b	
36	80.30 ± 1.83	81.20 ± 2.07	83.40 ± 1.14	78.00 ± 2.35	
48	81.00 ± 2.01	81.20 ± 2.07	83.20 ± 1.12	78.00 ± 2.35	

Significant differences within rows are indicated by ab (P < 0.05); No significant effect on kaliuresis; ^{NS}, Not significant; other abbreviations are as used in Table 1; (N = 10 per subgroup)

Table 6. Effects of Monotherapy with AML and HCZ on Serum Cl⁻ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)	Treatment Subgroups (Female)	Gender Effect
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	AML	HCZ	AML	HCZ	0.141 ^{NS}
0	130.60 ± 2.74	128.90 ± 2.16	130.80 ± 2.30	126.50 ± 2.65	
1	129.20 ± 2.29	125.10 ± 1.71	129.00 ± 2.41 ^a	122.30 ± 2.51 ^b	
3	126.60 ± 2.41	121.40 ± 1.75 _A	125.80 ± 2.40	119.60 ± 2.20 _A	
6	123.10 ± 2.62	117.20 ± 1.72 _B	122.70 ± 2.45 _A	117.60 ± 1.93 _A	
12	121.00 ± 2.61 _A	114.70 ± 1.69 _B	119.40 ± 2.46 _A	115.9 ± 1.91 _A	
24	118.80 ± 2.32 _A	113.40 ± 1.65 _B	116.60 ± 2.31 _A	114.60 ± 1.98 _A	
36	119.60 ± 2.38 _A	113.30 ± 1.76 _B	114.80 ± 2.21 _A	114.00 ± 2.18 _A	
48	119.60 ± 2.55 _A	113.60 ± 1.74 _B	114.50 ± 1.75 _A	113.80 ± 1.67 _A	

Significant differences within columns are indicated by AB and within rows by ab ($P < 0.05$): Significant treatment and time-dependent serum Cl⁻ loss are demonstrated; ^{NS}, Not significant; other abbreviations are as used in Table 1; (N = 10 per subgroup)

Table 7. Effects of Monotherapy with AML and HCZ on Urine Cl⁻ (mmol/L) in Type 2 Diabetic Hypertensive Subjects for 48 weeks

Week	Treatment Subgroups (Male)		Treatment Subgroups (Female)		Gender Effect
	AML	HCZ	AML	HCZ	
0	242.50 ± 5.07	244.00 ± 4.09	248.90 ± 2.31 ^a	235.50 ± 5.05 ^b	0.702 ^{NS}
1	244.50 ± 5.07	254.50 ± 5.11 _A	252.30 ± 2.84	245.80 ± 5.80	
3	248.20 ± 4.86 _A	259.80 ± 4.74 _A	253.60 ± 5.91	250.10 ± 5.91 _A	
6	251.10 ± 4.93 _A	251.50 ± 4.56 _A	264.50 ± 3.66 _A	243.70 ± 4.72	
12	253.50 ± 5.49 _A	247.70 ± 3.99	264.50 ± 3.20 _A	241.10 ± 4.63	
24	250.80 ± 5.13 _A	245.90 ± 3.97	260.40 ± 2.83 _A	239.00 ± 4.67 ^b	
36	248.00 ± 5.99 _A	244.90 ± 4.06	254.40 ± 3.61 ^a	237.70 ± 4.52 ^b	
48	234.00 ± 4.81 _A	244.00 ± 2.85 ^a	250.90 ± 3.58 ^a	236.00 ± 4.01 ^b	

Significant differences within columns are indicated by AA and within rows by ab ($P < 0.05$): There are significant treatment effects and time-dependent changes in urine CL⁻ excretion; ^{NS}, Not significant; other abbreviations are as used in Table 1; (N = 10 per subgroup)

4. Discussion

In the present study, 48 weeks of monotherapy with AML and HCZ led to changes in serum and urine electrolyte profiles. HCZ caused a mild hyponatremia which is the most common insidious metabolic derangement induced by thiazides [7]. This adverse effect is reported to be particularly common in elderly women after prolonged use of the drug [7,24], as evidenced in this study. Reduction in the diuretic dose or discontinuation of the diuretic together with liberalization of Na⁺ intake and, occasionally, restriction of water intake may correct this abnormality. Agreeably, we did not restrict salt intake in these subjects. Also, in these patients, the fact that hyponatremic changes were accompanied by increased natriuresis and diuresis, suggests that the patients were salt (Na⁺) sensitive. In fact, it has been reported that certain low-renin patient groups (e.g. blacks, the elderly, and diabetics) as well as those who manifest the metabolic syndrome are commonly more responsive to thiazide-type diuretic therapy [7,25,27]. Thus, salt sensitivity demonstrated in the diabetic patients in the current study suggests that salt restriction as a life-style adjustment may be beneficial in these patients as an adjunctive treatment of hypertension [20,21].

In contrast with AML therapy, HCZ therapy led to a significant but small i.e. 0.08-0.24mmol/L (2.00-5.74%) SK⁺ loss which became manifest from week 24 and the effect was more marked in F. However, there was no noticeable increase in kaliuresis and none of the patients developed clinical hypokalemia (SK⁺ < 3.5mmol/L). These observations may be most probably due to the effects of antidiabetic drugs or insipient nephropathy quite common in diabetics [3,26]. Another possible inference from the foregoing is that the etiopathogenesis of hypertension in these patients may not be due to hypokalemia, which contrasts with our findings [20,21] in a nondiabetic population from the same environment, but

to the metabolic syndrome, as evidenced by the relatively high BMIs of the study subjects.

Thiazide induced hypokalemia may worsen blood glucose control in diabetics or may possibly lead to the development of future new-onset diabetes (NOD) [6,7,8]. Thus, it is also generally recommended that diuretic-treated hypertensive patients should increase their daily intake of K⁺, although it is unclear whether such an increase may fully compensate for the kaliuretic effect of thiazides or provide meaningful additional BP reduction [20,21,25,26]. In our study, the moderate hypokalemia did not adversely affect blood sugar control in the trial subjects. This finding confirms the results of Okoro and Oyejola [17], who studied the long-term effects of HCZ on diabetic control and BP in Nigerians and reported that the drug was well tolerated and was associated with no clinically relevant changes in diabetic control or SK⁺ value. However, it is known that the diabetogenic effects of thiazides may not be noticeable until after 4-5 years the usual duration of most clinical trials [6,7,8]. Hence, this study and many others may be under-powered to detect this adverse prognostic impact on blood glucose. This is all the more reason why the benefits of the use of diuretics such as HCZ as first-line antihypertensive agents in younger hypertensive subjects be weighed against the risk of unwanted effects in the long-term. Furthermore, it has been well suggested that in diabetics and in subjects at increased risk of NOD (impaired fasting glucose, obesity, metabolic syndrome), diuretics should be used cautiously with the lowest effective dose and plasma glucose as well as serum electrolytes monitored periodically. Otherwise, they can be avoided entirely in at risk subjects with BP normalized by other safer classes of antihypertensive drugs [6,7,8].

Diuretics may cause several other adverse reactions, potentially leading to discontinuation which is about 83% more likely with HCZ than with AML [8,9]. Hypokalemia has also been suggested as a potential trigger of arrhythmias and sudden cardiac death [6,7,8], although its impact is now less than in the past because of the

widespread use of low-dose thiazides (as in this study), K⁺-sparing diuretics, and combinations with ACEIs or ARBs. Muscle cramps, which we did not observe in our patients, may cause suspicion of hypokalemia [6,7,25].

In the current study, AML caused no significant clinical biochemical abnormality in electrolyte profiles. Since, it is known that there is no one drug better than another all the time, therapy should be chosen on the basis of the single patient, considering the presence of subclinical organ damage, clinical cardiovascular disease, renal disease or DM which may be more favorably treated by some drugs than others and the presence of other disorders that may limit the use of particular classes of antihypertensives drugs [9]. In particular, AML, apart from exhibiting favorable biochemical effects on electrolytes, has additional biological effects not mediated through BP reduction, including antioxidant activity, inhibition of smooth muscle cell proliferation and enhancement in endothelial nitric oxide production [9,10,28].

An interesting observation in this study is that there appears to be gender differences in response to HCZ monotherapy in diabetic Nigerians because the F were consistently more responsive to the effects of HCZ than their M counterparts. This may be due to the effects of estrogens and androgens. To our knowledge, this is the first report of this nature in ethnic Nigerians and clinicians need to take note of this finding when treating these patients. Also, this is the first report in Nigeria that has compared the effects of AML and HCZ on electrolyte profiles during initiation of antihypertensive therapy in type 2 diabetic Nigerians.

5. Conclusion

Long-term AML monotherapy provides beneficial effects on BP and electrolytes and therefore represents a better option to initiate antihypertensive therapy in diabetic Nigerians. Also, low-dose HCZ therapy appears to cause moderate biochemical abnormalities such as hyponatremia and hypokalemia in diabetic Nigerians and is, therefore, a logical alternative to substitute for or add to AML therapy. However, caution should be exercised in making deductions from our data or extrapolating our findings to black hypertensive diabetic patients in general because of the small number of patients studied. Further research is necessary.

Competing Interests

The authors have no competing interests.

List of Abbreviations

1	ACEIs	Angiotensin converting enzymes inhibitors
2	ARB	Angiotensin receptor blocker
3	AML	Amlodipine
4	BMI	Body mass index
5	BP	Blood pressure

6	CCBs	Calcium channel blockers
7	DBP	Diastolic blood pressure
8	DM	Diabetes mellitus
9	F	Female/s
10	HCZ	Hydrochlorothiazide
11	M	Male/s
12	NOD	New-onset diabetes
13	SBP	Systolic blood pressure
14	SK ⁺	Serum potassium
15	SNa ⁺	Serum sodium

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