

Influence of West African Ethnicity and Gender on Beta-Cell Function and Insulin Sensitivity in Essential Hypertensives Treated with Hydrochlorothiazide and Hydrochlorothiazide-lisinopril Combination

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Abstract

Objective: To assess the effects of hydrochlorothiazide (HCT) given alone and in combination with an angiotensin-converting enzyme inhibitor (ACEI) on beta-cell function in a negroid population to further explore possible ethnic differences in the effect of antihypertensive drugs on homeostasis model assessment – insulin resistance (HOMA-IR). **Materials and Methods:** A total of 80 newly diagnosed Nigerian essential hypertensive patients were assigned to receive either HCT 25 mg daily or both HCT and lisinopril (Lis; 25/10 mg daily) in an open-label study for 12 weeks. The treatment groups were well matched in clinical and demographic baseline features. Changes in HOMA-IR from baseline to end of study (week 12), fasting plasma glucose (FPG), serum potassium, serum insulin, and blood pressure over the same period were also evaluated. **Results:** After 12 weeks, mean delta HOMA-IR (and %) was higher in the HCT monotherapy group; although, this change did not reach statistical significance in both groups -0.1 ± 7.1 , $P = 0.538$ (HCT) and 0.6 ± 4.2 , $P = 0.913$ (HCT + Lis); an insignificant increase was observed in FPG and serum insulin in both groups, whereas serum potassium decreased in similar fashion. Blood pressure reduction was similar in both groups. Analysis of HOMA-IR change according to gender in response to HCT mono- or combination therapy with Lis showed no significant difference. **Conclusions:** HCT monotherapy in hypertensive indigenous Nigerians, was not associated with worse metabolic effects when compared with combination therapy using Lis, an ACEI after 12 weeks. Low-dose thiazide diuretic as first-line antihypertensive medication may be safe in the short-term, further larger and long-term studies are needed to corroborate this finding.

Keywords: Angiotensin-converting enzyme inhibitor, blacks, essential hypertension, insulin resistance, thiazides

INTRODUCTION

Thiazide diuretics which form the bedrock of combination antihypertensive regimens in Africans and blacks have been shown to impair glucose tolerance on prolonged treatment.^[1] In contrast, inhibitors of the renin angiotensin system and angiotensin converting enzyme inhibitors (ACEI) in particular and especially lisinopril (Lis) improves glucose tolerance and prevents type 2 diabetes mellitus (T2DM).^[2] Despite these reports, it is not known if insulin resistance (IR) in untreated hypertensive Africans is affected by ethnicity. Although preliminary reports in normotensive African-Americans demonstrate no difference in homeostasis model assessment – IR (HOMA-IR) compared to whites, blacks had higher glycated hemoglobin,

impaired oral glucose tolerance test parameters and higher incidence of T2DM.^[3] It is thus unclear whether the effect of antihypertensive therapy on IR will exhibit any inter-ethnic differences. We found no report of any ethnic comparison of these drugs on IR in Africans. We, therefore, investigated IR and the impact of antihypertensive treatments on them in indigenous hypertensive Africans.

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In addition, IR and the effect of drugs on vascular reactivity are harbingers of vascular endothelial damage.^[4,5] IR is also associated with adverse left ventricular geometric concentric remodeling and left ventricular hypertrophy with worse prognostic outcomes.^[6] Thus, in addition to mitigating the adverse metabolic effects of concurrent thiazide therapy, evaluation of the impact of thiazide monotherapy and thiazide + Lis combination therapy on HOMA-IR may provide insight into potential prognostic implications of such combination therapies in black hypertensive nondiabetic patients. The aim of this study was to assess the impact of hydrochlorothiazide (HCT) on beta-cell and IR as well as any modification of this by Lis in Nigerian hypertensives. We also assessed the influence of ethnicity and gender on this.

MATERIALS AND METHODS

The design was a prospective open-labeled 12-week clinical study undertaken to evaluate the metabolic impact of thiazide diuretics (HCT) given alone and in combination with ACEI (Lis) in nondiabetic hypertensive subjects. The study was carried out at the Department of Medicine and General Outpatients Clinic of the Ladoko Akintola University of Technology Teaching Hospital (LTH), Oshogbo, Nigeria. LTH is a 200-bed tertiary health facility located in Oshogbo, the capital city of Osun State. Oshogbo is located in the tropical rain forest belt of Southwestern part of Nigeria and is about 200 km from Lagos the commercial capital city of Nigeria.

All participants gave written informed consent. The Research and Ethics Committee of LTH approved the study. A total of eighty consecutive subjects (convenient sample size) aged 40 years and above attending the hypertension clinic of LTH with a diagnosis of essential hypertension, that is, blood pressure (BP) $\geq 140/90$ mmHg (systolic BP [SBP] ≥ 140 mmHg and diastolic BP [DBP] ≥ 90 mmHg) on at least two occasions, were recruited for this study. Other inclusion criteria were fasting plasma glucose (FPG) ≤ 6.1 mmol/l and provision of written informed consent to participate in the study. The exclusion criteria were subjects with SBP > 170 mmHg and DBP > 110 mmHg; those with secondary hypertension, cardiac, or renal failure and those with known hypersensitivity to a study drug. In addition, pregnant women and those breastfeeding were also excluded from the study.

Subjects meeting the BP and other criteria for eligibility were entered into a 12-week treatment protocol and assigned into one of two treatment groups – HCT monotherapy 25 mg daily or HCT-Lis combination 25/10 mg daily. During this treatment period, those with persistently high BP (i.e., SBP ≥ 160 and DBP ≥ 100 mmHg) after the second visit (patients were seen every 4 weeks), were given calcium channel blocker (amlodipine) as a rescue drug. Amlodipine has been shown to have a neutral effect on blood glucose.^[7]

The primary end point was the change in HOMA-IR value from baseline to end of study (week 12). Changes in FPG, serum potassium, serum insulin, and BP over the same period were also evaluated.

Beta-cell function (BCF) was assessed using HOMA. Before treatment, blood samples were collected for FPG, insulin, lipid profile, electrolytes, urea, and creatinine. Baseline HOMA-IR value was calculated using the result of fasting plasma insulin at week 0. Blood samples were collected again after 12 weeks of therapy for the analysis of FPG, insulin, electrolytes, urea, creatinine, and the calculation of HOMA-IR.

Test instruments

HOMA is a computer-solved model used to predict the homeostatic concentrations which arise from varying degrees of β -cell deficiency and IR. Comparison of a patient's fasting value with the model predictions allows quantitative assessment of the contribution of IR and deficient β -cell to the fasting hyperglycemia (HOMA). It has been shown that the estimate of deficient BCF obtained by HOMA correlates with that derived using the hyperglycemic clamp and with the estimate from the intravenous glucose tolerance test.^[8]

HOMA is based on measuring plasma glucose and serum/plasma insulin.

The estimate of IR by HOMA score is calculated with the formula.^[9]

$$\frac{\text{Fasting serum insulin } (\mu\text{mol} / \text{ml}) \times \text{Fasting plasma glucose (mmol} / \text{L)}}{22.5}$$

With such a method, high HOMA score denotes high IR and low HOMA-IR values indicate low IR.^[9]

Serum insulin was measured using enzyme-linked immunosorbent assay technique using the Dako-Cytomation insulin assay method. It is based on two monoclonal antibodies. The microwell plate was coated with anti-insulin antibody. Simultaneous incubation of the sample and the enzyme-labeled antibody (conjugate) in the microplate formed a complex. A washing step removed the unbound enzyme labeled antibody. The bound conjugate was detected by reaction with the substrate 3,3',5,5' tetramethylbenzidine. The reaction was stopped by adding sulfuric acid (0.46 mol/l) to give a colorimetric endpoint that was read spectrophotometrically using a plate reader that read the 96-microwell plates of 8 strips at an absorbance of 450 nm.

Plasma glucose was determined using the hexokinase method, and serum electrolytes estimated using flame photometry absorption method of wavelength between 589 and 770 nm.

Analyses and statistical evaluation of data

Except where otherwise stated, results are expressed as means \pm standard deviation. Calculations and analysis were performed using the Statistical Package for Social Sciences,

version 16.0 (SPSS Inc., Chicago Illinois, USA). Statistical comparisons were made using the Student's *t*-test for unpaired variables. Chi-squared test was used for the comparison of proportions between the two groups. Differences between treatments were assessed using two-tailed Student's paired *t*-test for variables that were normally distributed. Relationships between continuous variables were assessed using Spearman's correlation. The value of $P \leq 0.05$ was considered statistically significant.

RESULTS

The study population comprised eighty subjects with essential hypertension who were assigned to receive either HCT alone or HCT/Lis combination. Baseline demographic characteristics were similar in the two treatment groups, patients who received HCT monotherapy had a mean age of 54.2 ± 8.0 years, whereas the HCT/Lis combination group had a mean age of 54.2 ± 8.1 years. Body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR) were comparable in both groups; although, many study participants were overweight or obese [Table 1].

Lis was studied because it is the long-acting ACEI with a duration of action similar to HCT. It is also the only ACEI that is in a fixed drug combination with HCT (zestoretic 25/10 mg) in our clinical practice. Angiotensin receptor blockers (ARB) such as losartan are not in wide usage in our setting due to cost.

Metabolic outcomes

There was an increase in HOMA-IR value from baseline to week 12, in the 2 treatment groups; although, the increase did not reach statistical significance, mean $\Delta -0.1 \pm 7.1$, $86 \pm 125.3\%$, $P = 0.538$ (HCT) and mean $\Delta 0.6 \pm 4.2$, $38.6 \pm 79.1\%$ $P = 0.913$ (HCT + Lis) [Table 2]. FPG increased from week 0 to week 12 in both groups, it increased by a mean of 0.3 ± 0.9 mmol/L in the HCT monotherapy and by

0.2 ± 0.8 mmol/L in the HCT-Lis group, the increase was not statistically significant. There was a statistically significant increase in fasting serum insulin in both treatment groups from baseline to end of the study. Fasting serum insulin levels for the HCT monotherapy group increased from 4.8 ± 2.8 to 6.2 ± 4.2 mU/ml ($P < 0.002$) and from 4.9 ± 2.7 mU/ml to 5.2 ± 3.0 mU/ml ($P < 0.004$) for the HCT-Lis group.

Among the HCT monotherapy group, there was a significant reduction in serum potassium from 4.1 ± 0.2 mmol/L at baseline to 3.9 ± 0.3 mmol/L at the end of study ($P < 0.003$); this represented a mean reduction of 5.7% over the 12-week. Similarly, combined HCT-Lis therapy also significantly reduced serum potassium from 4.1 ± 0.2 mmol/L at baseline to 4.0 ± 0.2 mmol/L at week 12 ($P < 0.003$). This represented a mean reduction of 4.5% over the 12 week [Table 2]. However, none of the subjects in either group had hypokalemia (serum potassium < 3.5 mmol/L) at the end of the study.

Analysis of HOMA-IR changes according to gender in response to HCT alone or HCT/Lis combination therapy showed no significant difference. Gender did not influence other metabolic outcomes [Table 3]. Furthermore, changes in HOMA-IR worsened with HCT only therapy, but improved nonsignificantly ($P = 0.567$) in the combination therapy group. Conversely, HOMA-insulin sensitivity (HOMA-IS) improved with combination therapy but reduced in HCT only therapy ($P = 0.055$) [Figure 1].

Blood pressure changes

Subjects who received combination therapy had a greater reduction in BP at the end of the study when compared with those who received HCT monotherapy. Both groups had significant reductions in SBP; 18.1 ± 15.3 mmHg in the combination group and 17.8 ± 10.8 mmHg in HCT monotherapy group ($P = 0.002$). During the study, three subjects among the HCT monotherapy group had amlodipine (a calcium channel blocker), added to their medication because of unsatisfactory reduction in their BP; this was carried out at the second clinic visit.

Table 1: Baseline demographics of study participants

	HCT monotherapy	HCT-lisinopril combination	P
Number of subjects	40	40	0.971
Age (years)	54.2 ± 8.0	54.2 ± 8.1	0.989
Gender			
Male	20	16	0.500
Female	20	24	0.369
BMI (kg/m ²)	27.9 ± 4.3	28.9 ± 5.3	0.344
WC (cm)	101.6 ± 11.0	104.5 ± 5.7	0.525
WHR	1.1 ± 0.2	1.1 ± 0.2	0.849
SBP (mmHg)	151.9 ± 9.1	151.9 ± 11.3	0.983
DBP (mmHg)	94.4 ± 6.9	93.1 ± 9.2	0.494
Mean pulse pressure	50.4 ± 9.0	49.0 ± 13.3	0.723
Mean ABP (mmHg)	113.7 ± 4.8	112.7 ± 8.4	0.552

BMI=Body mass index, WC=Waist circumference, WHR=Waist-hip ratio, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, ABP=Arterial blood pressure, HCT=Hydrochlorothiazide

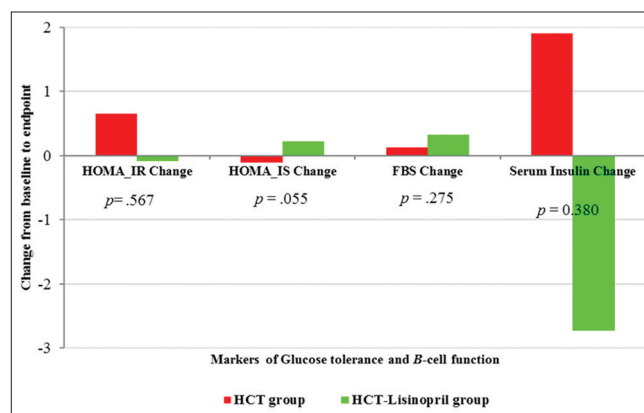


Figure 1: Comparison of the treatment groups according to change in B-cell function from baseline to endpoint

Table 2: Comparison of baseline and end of study B-cell function and serum potassium of study subjects

	Mean±SD		P	Mean±SD	
	Baseline	Endpoint		Change (Δ)	Percentage change
HCT only					
Fasting glucose	5.1±0.6	5.2±0.8	0.263	0.3±0.9	3.2±14.4
Serum insulin	4.8±2.9	6.2±4.2	0.002	-2.9±29.8	78.8±121.3
HOMA-IR	1.1±0.7	1.5±1.1	0.538	-0.1±7.1	86.0±125.3
HOMA-IS	75.4±61.7	107.6±122.7	0.428	0.0±1.0	-101.3±254.9
Serum potassium	4.1±0.2	3.9±0.3	0.003	0.2±0.2	5.7±5.6
HCT + lisinopril					
Fasting glucose	5.3±0.6	5.4±0.8	0.522	0.2±0.8	3.1±12.4
Serum Insulin	4.9±2.7	5.2±3.0	0.004	1.6±16.6	31.8±77.2
HOMA-IR	1.2±0.7	1.3±0.9	0.913	0.6±4.2	38.6±79.1
HOMA-IS	68.8±57.2	47.1±51.1	0.034	0.1±0.4	-14.0±135.0
Serum potassium	4.1±0.2	4.0±0.3	0.003	0.2±0.2	4.5±4.5

HOMA-IR=Homeostatic model assessment-insulin resistance, HOMA-IS=Homeostatic model assessment-insulin sensitivity, SD=Standard deviation, HCT=Hydrochlorothiazide

Table 3: Comparison according to gender of change in metabolic indices

Variable	HCT monotherapy group							
	Male (n=20)	Mean±SD	Female (n=20)	Mean±SD	F	P	95% CI	
Insulin (μU/L)	20	3.1±2.9	20	2.9±2.8	0.801	0.385	0.5-4.2	
HOMA-IR	20	1.3±0.1	20	1.1±0.2	0.894	0.359	0.8-1.5	
HOMA-IS	20	9.6±2.0	20	11.0±1.1	0.207	0.656	6.5-14.1	
FBG (mmol/L)	20	0.3±1.0	20	0.3±0.9	0.002	0.965	-1.1-1.5	
Potassium (mmol/L)	20	0.2±0.2	20	0.2±0.1	0.729	0.418	-0.1-0.4	
Variable	HCT/lisinopril combination group							
	Male (n=24)	Mean±SD	Female (n=16)	Mean±SD	F	P	95% CI	
Insulin (μU/L)	24	1.8±1.9	16	1.6±1.3	0.455	0.505	0.1-2.8	
HOMA-IR	24	0.8±3.8	16	0.6±4.0	0.000	0.996	-2.2-4.5	
HOMA-IS	24	6.1±0.4	16	6.0±0.4	2.917	0.098	5.7-7.0	
FBG (mmol/L)	24	0.2±0.8	16	0.2±0.7	2.101	0.158	-0.6-1.0	
Potassium (mmol/L)	24	0.2±0.1	16	0.3±0.1	0.144	0.708	-0.1-0.5	

FBG=Fasting blood glucose, HOMA-IR=Homeostatic model assessment-insulin resistance, HOMA-IS=Homeostatic model assessment-insulin sensitivity, SD=Standard deviation, HCT=Hydrochlorothiazide, CI=Confidence interval

DISCUSSION

The present study investigated in the short-term, the diabetogenic and other adverse metabolic potentials of thiazide diuretic monotherapy in Nigerians with essential hypertension as well as the possibility of amelioration of this effect(s) when combined with ACEIs. This study showed that after 12 weeks of therapy, there was no statistically significant change in IS in either of the two groups. Further, HCT monotherapy did not significantly affect IS as measured using HOMA-IR. Our results do not support the findings of previous studies comparing inhibitors of renin-angiotensin-aldosterone systems (ACEI or ARB) with HCT therapy, in which most study participants demonstrated worsening of IS as measured using HOMA-IR index with HCT monotherapy.^[10-12]

This absence of deterioration in HOMA-IR could be partly explained by the lack of development of hypokalemia in our

subjects. Hypokalemia, one of the metabolic derangements induced by thiazide-diuretics reduces insulin secretory ability through the adenosine triphosphate-sensitive K⁺ channels in Beta-islet pancreatic cells and worsens peripheral IS.^[13,14]

There are suggestions that preventing hypokalemia or keeping serum potassium between 4.0 and 4.5 mmol/L reduce or eliminate the risk of diuretic-induced dysglycemia or diabetes.^[12] Diuretic related reduction in serum potassium is typically dose-related and usually ranges from 0.2 to 0.6 mmol/L. In this study, the mean change in serum potassium was similar to these values, 0.3 ± 0.9 mmol/L for the HCT group and 0.2 ± 0.8 mmol/L in the HCT-Lis group; these represents a percentage change of 5.7% and 4.5% for the HCT monotherapy and combination therapy groups, respectively.

A similar potassium change was found by both Okoro *et al.*^[15] and Adigun *et al.*^[16] who used HCT to treat hypertension. Studies in which higher doses of up to 50 mg of HCT was

employed as monotherapy in hypertensives similarly showed the percentage change in plasma potassium of 4.9%.^[17]

When combined with ACEI enalapril (10 mg) with 50 mg HCT, a 7.9% fall in serum potassium was observed in hypertensive diabetic patients after 12 weeks of combination therapy, the fasting and postprandial plasma glucose likewise fell.^[18]

A meta-analysis of 59 studies involving 83 thiazide-diuretic treatment arms found a significant correlation between the degree of diuretic-induced hypokalemia and the increase in plasma glucose, and there was evidence that prevention of hypokalemia with potassium supplementation or potassium-sparing agents lessened the degree to which plasma glucose increased consequently to diuretic therapy.^[13] Thus, the change in plasma potassium appears to be related inversely to blood glucose change. The well-described effects of hyperkalemia in stimulating insulin secretion^[14,19] and insulin in inducing cellular uptake of potassium^[20,21] suggest that low plasma potassium could impair insulin secretion and thereby increasing plasma glucose.^[22,23]

The lack of significant change in potassium levels in our study does not support findings from a previous report suggesting greater hypokalemic effect of thiazide diuretics in American blacks.^[24] This lack of significant reduction in potassium levels may reflect the low-renin, volume-dependent nature of hypertension in Nigerians, which may alter K⁺ homeostasis in response to therapy in blacks^[25] or the relatively higher salt/potassium intake of the subjects studied.

IS was lower at 12 weeks in both treatment groups compared with baseline values. There was also a 10% reduction in IS in the HCT-monotherapy group compared with 4% reduction in the HCT-Lis combination group. There was a clear trend to Lis mitigation of IR following HCT. However, neither of changes attained statistical significance, probably reflecting a type 2 error. Similar worsening of IS with an increase in new-onset diabetes with thiazide diuretics was found in the Heart Outcomes Prevention Evaluation (HOPE) study.^[26]

The result of this study showed that body composition as measured by the WC, WHR and BMI as well as both SBP and DBP correlated positively with IR. However, diastolic BP and WC were the major contributors to IR as measured by HOMA-IR. This is consistent with the findings of several studies showing a positive association between IR and abdominal adiposity.^[27,28] Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization, often leading to T2DM. IR, the associated hyperinsulinemia and hyperglycemia, and adipocyte cytokines (adipokines) may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which constitute the metabolic syndrome and promote the development of atherosclerotic cardiovascular disease.

HCT/Lis combination therapy was more efficacious than HCT monotherapy in lowering BP. Adigun *et al.*^[16] have previously

made a similar observation among hypertensives in Ile-Ife, Nigeria. Previous studies have also shown that blacks have reduced BP responses to monotherapy with ACEIs or ARBs when compared to diuretic or calcium channel blockers but tend to respond better to a combination of ACEI and diuretics.^[9]

Study limitations

This study had clear limitations worth highlighting. First, no formal power calculations were undertaken to determine sample size to achieve 80% power at 5% alpha level to detect HCT versus HCT/Lis differences. There was a brevity of follow-up and we did not determine if any of our treated patients developed frank T2DM in this study. Ethnic differences will be better detected by direct comparison of black and white hypertensive patients in the same study, instead of historical data comparison. Nevertheless, the short-term safety of the drugs and lack of gender impact was seen in this study.

CONCLUSIONS

There was no statistically significant difference in the metabolic effects of compared to HCT/Lis combination, after 12 weeks of treatment in black African hypertensives. This however, represents short-term effects; as more pronounced effects of thiazide diuretics, and possibly also of ACEI, on BCF may occur in the longer term or at higher doses. The similarity observed in the metabolic impact of the two drug treatment groups may be due to the low dose of HCT employed. Larger and longer prospective studies are still required to further clarify the long-term safety and metabolic impacts/effects of thiazide diuretics in Nigerians with essential hypertension.

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Conflicts of interest

There are no conflicts of interest.

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