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# Risk Factors for the Development of Chronic Kidney Disease among Nigerians with Essential Hypertension

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This study sought to identify clinical parameters that may be risk factors for the development of chronic kidney disease in a population of hypertensive patients. This case control study examined non diabetic hypertensive patients with no identifiable cause of the hypertension. Two groups of hypertensive patients that were age and sex matched with similar duration of hypertension were classified into the CKD and control groups on the basis of the findings of markers of kidney damage and/or decreased creatinine clearance. Patients' hospital records of demographics, clinical and laboratory evaluations were used. Eighty patients with hypertension were studied of whom 40 had CKD and another 40 without CKD constituted the control group. The CKD group differed significantly from the control group with respect to; positive family history (65% versus 22.5%), cigarette smoking (62.5% versus 17.5%), BMI (24 versus 21 kg $m^{-1}$), hypertensive retinopathy grade III/IV (87.5% versus 17.5%), SBP (179 versus 168 mmHg), DBP (115 versus 101 mmHg) and uric acid (470 versus 200 μmol $L^{-1}$) Clinical features of positive family history of hypertension, history of cigarette smoking and findings of hypertensive retinopathy and uncontrolled hypertension with laboratory finding of hyperuricaemia are significant risk factors for the development of impaired renal function in Nigerian hypertensive patients.

**Key words:** CKD, hypertension, risk factors, progression

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## INTRODUCTION

Population based studies have shown that chronic kidney disease affects about 11% of the individuals in the US (Coresh *et al*., 2003) and 12% of the residents of Gröningen in the Netherlands (Zeeuw *et al*., 2005). Hypertension associated kidney damage is assuming epidemic proportions as it is considered one of the most common causes of end stage renal disease in Europe and the United States (Johnson *et al*., 2005; Valderrabano *et al*., 1998). Patients with essential hypertension have consistently elevated blood pressures above 140/90 mmHg with no identifiable cause. In the industrialized countries of North America and Europe patients with diabetes and hypertension constitute the majority of the End Stage Renal Disease (ESRD) population. The USRDS estimates that hypertension accounts for 27% of the population of the US residents that are receiving Renal Replacement Therapy (RRT) (USRDS, 2001). With increasing urbanisation and the consequent abandoning of the active way of life of the agrarian community to the sedentary lifestyle the developing countries of sub Saharan Africa and Asia are likely to experience an epidemic of non-communicable diseases such as hypertension and diabetes. The number of individuals with type 2 diabetes is likely to double worldwide with the developing countries accounting for the majority of the increase (King *et al*., 1998). The factors that have been linked to the development of Chronic Kidney Disease (CKD) and impaired renal function can be categorized into those that have been proven to be causal (risk factors) and those that have not been proven to be causal (risk markers). Hypertension has a unique place in the development of CKD in that it has been implicated as not only a progression factor but also an initiator factor for CKD. In addition the fact that the risk imposed by hypertension is modifiable at costs that can be afforded by even the poor hypertensive makes its effective treatment one of most cost effective interventions in medical practice. Even when available the cost of RRT is prohibitive and as a result patients who require treatment cannot afford it on a sustainable basis. Ninety percent of the estimated 1 million individuals on RRT reside in the developed countries (Lysaght, 2002) where about 5% of the health budget is spent by the less than 1% of the general population requiring dialysis and renal transplantation in the US and 2% in Europe. Moreover the projected number of 2 million individuals on RRT by 2010 will make funding their health care cost difficult for even the rich countries (Xue *et al*., 2001). Identification of risk factors for the loss of renal function and the subsequent institution of preventive measures will reduce the burden of the care of ESRD patients on the already overstretched healthcare resources of the poor countries. In the search for ways to lessen the burden of CKD in Nigeria we embarked on this study in order to identify risk markers and factors for CKD among the large population of essential hypertensives who should be target for more intensive treatment with the aim of preventing them from developing CKD and/or progression to ESRD.

## MATERIALS AND METHODS

This case control study involved 80 adult Nigerian hypertensive patients who were made up of 40 persons with features of CKD that were age and sex matched against another 40 who had normal GFR without any markers of kidney damage. Clinical and laboratory evaluations of the patients were carried out at the Obafemi Awolowo University Teaching Hospital Ile Ife Nigeria. We recorded the patients´ age and sex and enquired into the patients family history for hypertension and diabetes and social history of cigarette smoking and alcohol drinking. The personal history of the hypertension was documented including such details as the duration, complications that developed during its course, compliance to the prescribed antihypertensive drugs. On compliance to treatment we relied on the patients account on how regularly they used their drugs. The blood pressure we recorded was the mean of the different measurements on hospital visits. Height and weight measurements were used to calculate the Body Mass Index (BMI) of the patients. We recorded the laboratory and radiologic investigations such as dipstick urinalysis for protein and blood urine microscopy for abnormal constituents, Chest X Ray (CXR), Electrocardiography (ECG) echocardiography ultrasound of the kidneys, serum, electrolytes, urea and creatinine and the determination of creatinine clearance (CCl) by measurement from 24 h urine collection. We categorized the hypertensive patients into 2 groups namely the Chronic Kidney Disease (CKD) and the control groups based on the presence or absence of proteinuria and/or haematuria, for the CKD and the control groups, respectively. The CKD group also had CCl of less than 60 mL $min^{-1}$ and/or serum creatinine concentration of greater than 135 μmol $L^{-1}$ and urinary protein excretion rate not exceeding 1 g in 24 h while the controls had normal urinalysis, urine microscopy and Ccl of greater than 60 mL $min^{-1}$. We excluded hypertensive patients with clinical or laboratory features suggestive of glomerulonephritis, diabetes obstructive uropathy, nephrolithiasis and other causes of secondary hypertension. Excessive analgesic usage and diagnosis of gout were additional exclusion criteria for both the CKD and control groups. All the patients had essential hypertension for greater than 5 years and were older than 40 years.

**Statistical analysis:** The values of the parameter were expressed as means and standard deviation. Chi-square test was used to compare the groups and p-values greater than 0.05 were considered as significant.

## RESULTS

**Demographics and patient characteristics:** The study involved 80 hypertensive patients aged 40 years and above that were categorized into two groups. The CKD group had 40 patients that were made up of 32 male and 8 females with an age range of 40-76 years and mean age of 51.4±8.8 years while the control group of 40 patients (24 males, 16 females) had a mean age of 55.1±8.6 years and a range of 40-71 years (Table 1). Whereas the male: female ratio was 4:1 in the CKD group, it was 3:2 in the control group (Table 2). Family history of hypertension was present in 26 (65%) of the CKD group compared to 9 (22.5%) of the control group. Significantly less proportion of patients in the CKD group responded that they complied strictly with their antihypertensive medication (Table 3). The hypertensive patients in the CKD group were more likely to have smoked cigarette than those in the control group and a similar observation was noted for the regular use of alcoholic breverages (Table 4).

**Clinical measurements:** The mean Body Mass Index (BMI) in the CKD group of 24.1±3.6 kg $m^{-2}$ was significantly greater than that of the control group of 21.2±2.6 kg $m^{-2}$, p<0.0002. The average duration of the hypertension was similar in both the CKD and control groups being 10.0±5.16 years versus 9.18±3.8 years for the CKD and control groups, respectively (p<0.8). The average Systolic Blood Pressure (SBP) differed between the groups with that of the CKD group (179.0±17.7 mmHg) being significantly higher than that of the control group (168.38±12.8 mmHg), p<0.0005. The CKD group also had significantly higher diastolic blood pressure (DBP) than the control group; with their respective mean DBPs being 115.18 mmHg versus 101.05 mmHg, respectively (Table 5). Consequently the average SBP, the DBP and mean arterial BP were all higher in the CKD group than the control group (Table 5). Fundoscopic evidence of stages III/IV hypertensive retinopathy (Keith-Wagner classification) was present in 35 (87.5%) of the CKD group and in 7 (17.5%) of the control group.

**Investigation results:** A comparison of the CKD and the control groups with respect to the biochemical parameters is depicted on Table 6. The CKD group had significantly higher serum creatinine, haematocrit (pcv), but similar serum cholesterol.

Tables 1: Age matching of the CKD versus the control groups

| Characteristic | CKD | Control |
|---|---|---|
| Age range (years) | 40-76 | 40-71 |
| Mean age (years) | 51.4 | 55.8 |
| p = 0.06 | | |

Table 2: Sex distribution among the groups

| Sex | CKD | Control |
|---|---|---|
| Male | 32 | 24 |
| Female | 8 | 16 |
| Total | 40 | 40 |
| $\chi^2 = 38.09$, p =0.005, df = 1 | | |

Table 3: Compliance of patients to treatment

| Compliance | CKD | Control |
|---|---|---|
| Good | 15 (37.5) | 30 (75) |
| Poor | 25 (62.5) | 10 (25) |
| $\chi^2 = 11.43$, df = 1, p = 0.0001 | | |

Table 4: Smoking and alcohol usage among the groups

| Habit | CKD | Control |
|---|---|---|
| Smoking | | |
| Present | 25 (62.5) | 7 (17.5) |
| Absent | 15 (37.5) | 33 (82.5) |
| $\chi^2 = 16.88$ df = 1, p = 0.0001 | | |
| Alcohol | | |
| Present | 25 (62.5) | 8 (20) |
| Absent | 15 (37.5) | 32 (80) |
| $\chi^2 = 14.91$, df = 1, p = 0.0001 | | |

Table 5: Blood pressure means and ranges among the groups

| Blood pressure (mmHg) | CKD | Control |
|---|---|---|
| SBP mean (SD) | 179(17.69) | 168.3 (12.8) |
| SBP range | 160-220 | 150-200 |
| p = 0.005 | | |
| DBP mean (SD) | 115.18(9.95) | 101.05 (6.8) |
| DBP range | 100-130 | 90-120 |
| p = 0.0001 | | |

Table 6: Laboratory parameters of the groups

| Parameter | CKD | Control | p-value |
|---|---|---|---|
| Serum creatinine (μmol $L^{-1}$) | | | |
| Mean (SD) | 569.7 (425.7) | 94.2 (18.7) | <0.0001 |
| Range | 185-1932 | 66-125 | |
| Creatinine clearance (mL $min^{-1}$) | | | |
| Mean (SD) | 35.15(15.2) | 84.15(17.6) | <0.0001 |
| Range | 2-58 | 63-121 | |
| Serum uric acid (μmol $L^{-1}$) | | | |
| Mean | 470 (110) | 280 (100) | <0.0001 |
| Range | 200-72 | 160-540 | |
| Haematocrit | | | |
| Mean (SD) | 28.6 (5.5) | 32.6 (2.9) | <0.0001 |
| Range | 17-43 | 25-40 | |
| Serum cholesterol | | | |
| Mean (SD) | 5.04 (0.81) | 5.28 (0.74) | <0.24 |
| Range | 3.4-6.7 | 3.2-6.8 | |
| Serum urea | | | |
| Mean (SD) | 11.0 (5.7) | 4.04 (0.9) | <0.0001 |
| Range | 3.2-25 | 2.4-5.4 | |

## DISCUSSION

In this study we identified among patients with essential hypertension differences in characteristics between those who developed Chronic Kidney Disease and those who maintained normal kidney function although the duration of the hypertension was similar in both groups. The conventional cardiovascular risk factors such as age, male sex, elevated blood pressure, high serum cholesterol, cigarette smoking, high body mass index and diabetes have been shown to be deleterious to the kidneys (Fox *et al*., 2004). The relatedness of CV and kidney outcomes has also been highlighted in both the hypertensive and general populations in which impaired kidney function was associated with adverse CV end points (Mann *et al*., 2001). Some researchers have pointed to a growing evidence of the existence of hypertension in two forms that ultimately determines the renal and CV outcomes. Salt sensitivity with loss of nocturnal dipping and presence of albuminuria describe a subset of hypertensives with elevated risk of end organ damage (Bigazzi *et al*., 1994) whereas the absence of those features would predict favourable renal outcome of the essential hypertension. It thus appears that salt sensitivity or conversely salt resistance maybe the basic difference between the group of essential hypertensives who would or would not develop kidney disease. In our study both the CKD and the control groups had similar ethnicity with all of them being black Africans from Nigeria. Studies from the United States suggest that the black race is at increased risk of developing CKD with estimates that there may be a threefold increase in risk among African Americans compared to their Caucasian counterparts (Bakris *et al*., 1997). The increased risk of hypertension related kidney damage in the black race is not accounted for by either greater prevalence of hypertension, greater severity or lower socio-economic status (Freedman *et al*., 1993). The higher risk of kidney damage and indeed other end organ damages may be associated with genetically determined and/or environmentally induced exaggeration in the profibrotic mechanisms (Bloem *et al*., 1995).

In this study 51 years was the mean age of the patients who developed CKD a figure that is comparable to the 50 years that was reported by Marcantoni *et al*. (2002) of biopsy proven hypertensive nephrosclerosis in African Americans. Marcantoni *et al*. (2002) also noted that African Americans tended to develop hypertensive nephrosclerosis earlier than their American Caucasian counterparts. The African American Study of Kidney disease (AASK) pilot study had shown good concordance between the clinical diagnoses and biopsy proven diagnosis of hypertensive nephrosclerosis thus greatly supporting our assumption that our CKD group would have had hypertensive nephrosclerosis confirmed if biopsies were done. Poor compliance to the antihypertensive prescription was noted to be a risk factor for the development of CKD in our study. While most Nephrologist agree that malignant hypertension if untreated can rapidly cause CKD there is disagreement on the matter of essential hypertension leading to deterioration in renal function. Ojo *et al*. (1992) had reported in an autopsy series of 66 chronic renal failure patients in Nigeria a 16.6% rate of malignant nephrosclerosis and 7.6% benign nephrosclerosis thus implying that the majority of the Nigerians with hypertension associated CKD suffered malignant hypertension. Our study showed that 87.5% of the CKD group had fundoscopic evidence of advanced hypertensive retinopathy thereby further corroborating the report of Ojo *et al*. (1992). That observation does not detract from our position that poor drug compliance remains a risk factor for CKD. The role of uncontrolled hypertension as an important determinant of the rate of progression of CKD is well accepted (Pugley, 2005). Closely related to compliance is the issue of poor blood pressure control that was seen in our study. Both the mean systolic and diastolic blood pressures in the CKD and the control groups were above the normal blood pressure in adults of less than 140/90 mmHg. The differences between the systolic pressures of the CKD and the control groups and the diastolic pressures of the groups were statistically significant. Marcantoni *et al*. (2002) reported that the mean arterial pressures were not different between Caucasians and AA whereas the later developed HTN more than a decade earlier than their Caucasian counterparts. Present study suggests that the more severe the hypertension the greater is the risk factor for the development and progression of impaired renal function and this in keeping with previous studies (Toto *et al*., 1995; Klag *et al*., 1993). The family history of hypertension was positive in 65% of the CKD group in our study and a similar rate of 70% was seen in African American with hypertensive nephrosclerosis (Marcantoni *et al*., 2002) while in our control group the rate was 22.5%. It appears from this study that a positive family history is a risk marker for the development of CKD thereby indicating a genetic predilection to development of impaired renal function. Studies in African American who have high prevalence rate of both hypertension and CKD have shown that there is a familial risk of developing CKD (Freedman *et al*., 1993; Fergusson *et al*., 1988). A possible genetic link between hypertension and CKD may lie in the renin angiotensin system in which specific

polymorphisms have been associated with diseases of the kidneys and the cardiovascular system. Whereas mutation of the angiotensinogen gene has been related to essential hypertension, the homozygous DD genotype of the angiotensin converting enzyme has been associated with impaired renal function in hypertensives (Fernadez-Llama *et al*., 1998). Cigarette smoking was significant among the group of CKD patients in our study again supporting earlier reports that the social habit is implicated in the progression of CKD. It has been reported that the risk of developing ESRD among smokers was 5 times greater than in the general population (Orth and Ritz, 2002). We observed that the CKD group had significantly higher uric acid levels than did the control group. There is in recent times increasing evidence suggesting that hyperuricaemia is an independent risk factor for development of impaired renal function as was reported in South east Asia (Domrongkichaiporn *et al*., 2005). The salt sensitive hypertensives who are at increased risk of developing progressive renal disease are also likely to be blacks with gout or hyperuricaemia. It appears that hyperuricaemia and/or low nephron mass are the pathogenetic mechanisms that cause impaired renal function in patients with mild to moderate hypertension (Johnson *et al*., 2005).

## CONCLUSIONS

There is the need to identify from among the very large number of individuals with essential hypertension world wide those patients that are at high risk of developing impaired renal functions for early and intensive treatment to prevent, retard or even regress the kidney disease. Our study has shown that among Nigerian hypertensive patients, a positive family history of hypertension, poor compliance to prescribed antihypertensive agents and poor blood pressure control, cigarette smoking and findings of hypertensive retinopathy, hyperuricaemia indicate that such patients are at risk of hypertension related kidney disease. These indices can easily be detected and measures instituted to reduce the overall number of people requiring renal replacement therapy as a result of hypertensive nephrosclerosis.

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