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The relationship between kidney and hypertension: a review

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Summary

For several decades clinicians and researchers have come to recognize the crucial role played by the kidney in the control of blood pressure. Richard Bright in the past had noted that patients with chronic kidney disease often showed evidence of left ventricular hypertrophy and arteriosclerosis. Fredrick Mohamed and Sir William Gull later demonstrated that elevation of blood pressure might occur even in patients with no evidence of kidney disease. There are now hypotheses to support the fact that even primary hypertension has its origin in the kidney. The consequence of hypertension of the kidney is chronic renal failure; Prevalence rates of CRF range from 25 –100 per 100,000 populations and the incidence continues to grow increasingly at a rate of about 8-10% per year thereby posing a major public health problem especially in the developing countries. Management of chronic renal diseases is tedious and very costly. The consequence of the association between kidney and hypertension on the patient, the family, the national economy of a country and the society at large is considerable, hence the need to evolve preventive strategies.

Keywords: *Relationship, kidney, hypertension*

Résumé

Plusieurs mèdecins et chercheurs ont reconnus le role crucial des reins dans le controle de la pression arterielle. Richard Bright dèmontrait que les patients ayant une chute des reins chroniques avaient une èvidence d'hypertrophie ventriculaire gauche et artèriosclerose. Des deux dèfunts Frederick Mahomed et Wilians Gull dèmontraient que l'èlèvation de la pression artèrielle apparaient aussi aux patients n'ayant pas de problèmes des reins. Il y a maintenant des hypothèses qui supportent le fait que l'hypertension primaire a son origine des reins. Les consèquences de l'hypertension induit la chute chronique de reins. Les taux du CRF varie de 25-100 par 100,000 personnes et une incidence croissante de 8-10% , posant un problème de santè publique majeur en pays sous-dèvelopès. Le management des cas chroniques est difficile et cher. Les consèquences de l'association-rein-hypertension sur le patient, la famile et l'èconomie nationale du pays est considerablement grande, nècessitant des stratègies prèventives.

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Introduction

The principal functions of the kidney include maintenance of volume, excretion of metabolic waste products, detoxification and elimination of drugs, control of red blood cell mass through production of erythropoietin, endocrine control of mineral metabolism and maintenance of acid base balance. However, renal dysfunction is often associated with loss of blood pressure control, which makes it possible to debate whether the kidney is primarily engaged in the development of essential hypertension. On the other hand, untreated hypertension often leads to complications such as cerebrovascular disease, cardiac hypertrophy, cardiac failure, retinopathy, and kidney failure. This paper reviews the relationship between these two entities.

The kidney

The kidneys are located retroperitoneally with their upper poles and lower poles opposite the twelve thoracic and third lumbar vertebrae respectively. The right kidney is generally lower than the left. Each adult kidney may weigh about 130-170gm and may measure about 12 by 6 by 3cm [1]. A single artery originating from the aorta usually supplies each kidney. A corona section of the kidney reveals two distinct regions, the medulla and the cortex. The kidney may contain up to about 1,200,000 nephrons, each of which is a functional unit. The principal functions of the kidney include but not limited to the following maintenance of volume, excretion of metabolic waste products, detoxification and elimination of drugs, control of red blood cell mass through production of erythropoietin, endocrine control of mineral metabolism and maintenance of acid base balance. In maintaining its function the kidney possesses some natural barriers, which prevent the kidney from losing many of the substances that it filters. These structures are:

1. Glomerular capillary endothelium
2. Glomerular basement membrane,
3. Visceral epithelium
4. The mesangium

Increased urinary excretion of substances, especially protein by the kidney is therefore seen and often interpreted as a sign of kidney disease.

Hypertension

According to the WHO/ISH, hypertension is the elevation of blood pressure up to and beyond a systolic blood pressure of 140mmHg and or diastolic blood pressure of 90mmHg [2] (Table 1). Untreated hypertension often leads to complications such as cerebrovascular disease, cardiac hypertrophy, cardiac failure, retinopathy, and kidney fail-

ure. Hypertension is one of the most important non-communicable diseases worldwide. In spite of the increasing public awareness program and rapidly increasing array of antihypertensive agents, hypertension remains one of the leading public health problems in many parts of the world. Arguably, it is the most prevalent cardiovascular disorder the world over [3]. The prevalence of hypertension increases with age and practically in all age groups and subpopulations except in a few pockets of population where people are said to be living very close to nature [4]. It is also believed to be more prevalent in Blacks than in whites. This difference has been blamed on factors such as heredity, salt intake and greater environmental stress. Hypertension has also been shown to be more common in both extremes of the socioeconomic class.

Table 1: 1999 WHO/ISH guidelines on management of hypertension

	SBPmmHg		DBPmmHg
Optimal	<120	and	<80
Normal	<130	and	<85
High normal	130-139	and/or	85-89
Hypertension			
Grade 1	140-159	and/or	90-99
- Borderline	140-149	and/or	90-94
Grade 2	160-179	and/or	100-109
Grade 3	>180	and/or	≥110
Isolated SHT	≥140	and	< 90
- Borderline	140-149	and	< 90

Hypertension can be primary/essential, which has no known cause and may account for about 95% of cases or secondary, which has known causes, and account for only about 5% of all the cases of hypertension. Secondary hypertension include reno-vascular and renoparenchymal diseases, adrenal cortex and medulla problems e.g Cushing's disease, pheochromocytoma and primary hyperaldosteronism. Others will include coarctation of aorta, thyrotoxicosis and rennin secreting tumors. There are now hypotheses to support the fact that even primary hypertension has its origin in the kidney [5]

Association between Kidney and Hypertension.

The association between the kidney and hypertension dated back to 1876 when Richard Bright first called the world's attention to the existence of a destructive relationship between kidney and blood pressure [6]. Bright had noted that patients with chronic kidney disease often showed evidence of left ventricular hypertrophy and arteriosclerosis. He concluded that this might have reflected the increased force required to drive blood through a disease vasculature. Fedrick Mahomed and Sir William Gull later demonstrated that elevation of blood pressure might occur even in patients with no evidence of kidney disease [7]. Sir William Gull concluded that the arterial fibrosis noted in patients with hypertension could not be caused by kidney disease.

For several decades clinicians and researchers have come to recognize the crucial role played by the kidney in the control of blood pressure. However, the fact that renal dysfunction is often associated with loss of blood pressure control, makes it possible to debate whether the kidney is primarily engaged in the development of essential hypertension. In this regard, the kidney could affect systemic blood pressure via changes in sodium excretion or by modifying the release of some vasoactive substances. This role played by the kidney has been related to the disturbance in the renal heamodynamics. It has been suggested that a fall in renal perfusion may be the initiating process in the development of essential hypertension and it is believed to begin in the pre-hypertensive stage. It is therefore very tempting to say that renal hypoperfusion is a very early sign and perhaps a prerequisite for the development of essential hypertension, thus an inverse relationship may exist between the level of blood pressure and renal blood flow. However a possible confounder in this relationship is the age since it is difficult to say whether the reduced renal blood flow in the elderly hypertensive is due to age or hypertension. Evidences abound to show that the reduced renal blood flow with age is steeper for hypertensives than in normotensives. Experimental models of genetic hypertension have also shown that the inherited tendency to develop essential hypertension resides in the kidney. For example, animal and human studies have shown that a transplanted kidney from a hypertensive donor raises the blood pressure and increases the need for antihypertensive treatment in recipient coming from normotensive families [5]. Conversely, a kidney from a normotensive donor does not raise the blood pressure in the recipient. Other researchers have also suggested that essential hypertension may be due to an inherited abnormality of sodium handling by the kidney. This defect is believed to be mediated by genetic alterations in the expression or regulation of transport mechanism involved in sodium reabsorption or excretion [5]. Indeed, the kidney is one of the main targets of hypertensive process and hypertension is both a cause and a consequence of kidney disease. Regardless of the aetiology, hypertension is a significant determinant of progression of kidney diseases. Hypertension is also well known to be associated with increasing incidence of diabetic nephropathy, leading to progressive decline in renal function. The kidney may also cause hypertension via nephritis, renal artery stenosis, polycystic kidney disease and renal failure. In fact the number of nephrons in the kidney at birth has been shown to have a relationship with development of essential hypertension in later life [5]. A recent autopsy study found that people with essential hypertension had nearly 50% fewer nephron number compared to control subjects [8]. A reduced nephron number often results in compensatory

hyperfiltration, which may lead to progressive nephron loss over time, decreasing ultrafiltration surface area and thereby limiting sodium excretion. Earlier on, Barkers and others had previously identified a strong relationship between intrauterine growth retardation and low birth weight with later development of primary hypertension in adult [9]. Both low birth weight and intrauterine growth retardation have been consistently shown to correlate with renal impairment and reduced nephron number. Further more, serum uric acid has been shown to also correlate with low birth weight and reduced nephron number [10]. The above represents the relationship and interaction between the kidney and primary hypertension.

Hypertension in renal failure

Several factors may be responsible for the cause and maintenance of hypertension in renal failure. Some of these include alteration in structure of the compliance vessels, which may become stiff and hypertrophied. Increased vasoactive substances like endothelin and possibly low vaso depressors like PGE2, which may increase peripheral resistance. Neural influence as reflected by high levels of noradrenaline and adrenalin in the pre-dialysis period may also contribute to high blood pressure in renal failure. The issue of salt and water retention is perhaps the most clearly understood of all these factors. The incidence of hypertension in subjects with CRF is therefore higher than in normal population and by the beginning of dialysis it may be up to 70-80% [11]. Hypertension has a particularly high incidence in patients with autosomal dominant polycystic kidney disease and there is an earlier onset of hypertension in these subjects compared to normal population. It may be as high as 70% among them [11]. Glomerulonephritis is a common kidney disease and it manifests by proteinuria, heamaturia, fluid retention and hypertension. In patients with glomerulonephritis and renal insufficiency prevalence of hypertension may be as high as 18-65% even with normal or near normal renal function [12]. This figure may fall drastically with regular dialysis. Hypertension is therefore clearly seen as one important risk factor for the progression of renal disease. Earlier studies have demonstrated that control of blood pressure decreases the rate of increase in serum creatinine and improved survival in patients with glomerulonephritis and pyelonephritis [12]. Frequent clinic visits and better blood pressure control retarded progression of kidney diseases. It is therefore not surprising that a lower target of 120/75mmHg for control of hypertension was set for patients with chronic renal disease [2].

Kidney involvement in hypertension

One of the current problems with classification of renal failure is the distinction between renal failure due to hypertension and that due to primary renal diseases. This problem is further compounded by the fact that difficulty exists in proving that non-malignant hypertension or benign essential hypertension can lead to renal failure. While malignant hypertension is a clear culprit in the causation of hypertensive renal failure, opinion however differs with regards to non-malignant hypertension. Kadiri *et al* in a study of 56 subjects with malignant hypertension have shown that malignant accelerated hypertension was associated with high morbidity, especially renal failure; it primarily afflicted patients in their prime years and known survival at one year was 37.5% [13]. Historically, the natural history of untreated hypertension over a period of 20 years follow up in one study has been shown to result in renal complication in up to 42% of cases and renal failure in 10% [14]. In the first Veteran Administration Cooperative study, 4% of 70 patients with diastolic blood pressure in the range of 115-129mmHg developed renal insufficiency over an average of 1.3year follow up. This contrasted with 2% of about 194 subjects in a similar study who developed renal insufficiency with diastolic blood pressure of 90-114mmHg over an average of 3.3 years follow up period, suggesting that the level of blood pressure may determine the degree of renal insufficiency. Deterioration in renal function has also been observed in up to 15% of patients on treatment for essential hypertension. Hypertension is a leading cause of kidney failure in the US, accounting for 25 percent (87,000) of the nearly 379,000 people treated for kidney failure in 2000, while in Nigeria it is close to 45 percent [15,16,17]. Black Americans are six times more likely than whites to develop kidney failure from hypertension and account for 32 percent (122,000) of all treated patients [15].

Hypertensive nephrosclerosis is more commonly seen in men, black race, older individuals and people with persistently severe hypertension. In a previous study here in Nigeria, which looked at hypertension induced renal failure (HICRF), it was concluded that HICRF is a major cause of mortality; renal failure is often advanced at presentation, and blood pressure is usually in the accelerated phase. Significant cigarette smoking, severe headache necessitating consumption of significant quantity of analgesics, and a family history of hypertension were striking features [18]. Hypertension therefore influences the progression of chronic renal disease significantly, perhaps to consolidate the relationship between it and the kidney. This may be done in some or all of the following ways.

1. The earliest stages involve a fall in renal blood flow resulting in increased renal vascular resistance but the glomerular filtration rate is preserved.
2. Renal impairment then follows with damage to glomerular and pre-glomerular vessels leading to ischaemia and loss of glomerular function.
3. The normal loss of glomeruli, which occurred with age, progress at a faster rate in hypertensive subjects.
4. High systemic pressure is also transmitted to the glomerulus, leading to intraglomerular hypertension, hyperfiltration and damage to both glomerulus and the tubule.

Several markers of renal involvement in hypertension have

been identified to follow the above mechanisms. These include

Hyperuricemia
N-acetyl-beta-glucosaminidase
Microalbuminuria.

Of these parameters, microalbuminuria is the most studied. In diabetes mellitus, microalbuminuria predicts the development of overt nephropathy and screening of diabetic patients for this condition is now a recommended practice [19]. In hypertensive subjects, recent evidences suggest that microalbuminuria is prevalent in non-malignant hypertension and may predict the development of overt proteinuria and therefore chronic renal disease, as continuous excretion of protein in the urine increases nephrosclerosis. In a recent study, Olatunde *et al*, studied microalbuminuria in sixty-nine hypertensive subjects, prevalence of microalbuminuria in that study was 17.4% and microalbuminuria correlated positively with systolic blood pressure, serum urea, serum craetinine and retinopathyl [20]. The study concluded that microalbuminuria is associated with microvascular complications, poor cardiovascular and renal status. It should therefore be in order to recommend that urinary albumin excretion should become a routine clinical examination for subjects with hypertension as this early marker is often subsequently accompanied by overt proteinuria; decrease urinary concentrating ability and further reduction in the glomerular filtration rate.

In the early stage of involvement of hypertension in the kidney, the kidney appears normal. Clinical evidence of this involvement is often scanty but patients with long duration of hypertension may have vascular abnormalities consistent with nephrosclerosis in the presence of near normal renal function. The most common vascular lesion in hypertensive renal disease is arteriosclerosis of the afferent and efferent vessels and glomerular tuft. The gross appearance of the kidney depends on the severity of hypertension and the extent of vascular changes consequent on the elevated blood pressure. In advanced cases however, both kidneys are coarsely granular with capsule stripping with difficulty and this is the stage signaling the development of chronic renal failure. At end stage the kidneys appear shrunken. Microscopy reveals arteriosclerosis of the arcuate and interlobar arteries. The afferent and efferent vessels show fibrous thickening of the intima, fraying and splitting of the internal elastic lamina of the medium size arteries with consequent widespread narrowing of the small vessels. There is usually a concomitant thickening of the glomerular capillary tuft and the corresponding tubules become atrophic. Functional changes at this stage include initial but transient increase in glomerular filtration rate with subsequent reduction in this parameter. This is then followed by increased tubular dysfunction, resulting from tubular atrophy with decreasing reabsorptive capacity and increased urinary loss of fluid. Thereafter, overt renal failure begins. It is pertinent to say that the microscopic appearance of the "end stage kidney" is similar regardless of cause, which is why a biopsy in a patient with chronic renal failure yields little useful information.

All over the world, hypertension on its own causes significant morbidity and mortality and most hypertensive deaths are due to cardiovascular diseases and renal failure [3,15]. Hypertension occurs in many renal diseases and it is also well known that a rise in blood pressure may be associated with renal damage. This often results in long-term failure despite control of the blood pressure. Hypertension is therefore still seen as one of the most frequent causes of end stage renal failure the world over. Majority of the patients often present late with cardiovascular diseases and renal failure. In Nigeria, hypertension accounts for between 25 % and 43% of all cases of end stage renal failure [16,17]. The consequence of hypertension in the kidney is chronic renal failure; it is characterized by progressive and irreversible loss of renal function leading to accumulation of nitrogenous waste products of metabolism, which are normally excreted, into the urine. Prevalence rates range from 25 –100 per 100,000 populations and the incidence continues to grow increasingly at a rate of about 8-10% per year thereby posing a major public health problem, especially in the developing countries [21]. In some studies, it accounted for between 2-8% of hospital admissions [21]. In the USA hypertension is the second most common cause of renal failure, about 74% of adult black Americans are aware of their hypertension status while only 57% are on treatment and 14-25% of them are controlled [22]. In Nigeria, only a third of the hypertension populations who are aware of their disease are on any form of treatment. Generally between 25 and 38% of the hypertensive population in Nigeria are controlled [23,24]. Lack of treatment therefore leads to the development of persistently and severely elevated blood pressure, which often heralds chronic renal failure. It is therefore not surprising that hypertension is responsible for many cases of CRF. Untreated CRF by definition is universally fatal and patients with CRF represent a group of people with higher mortality compared with the general population, even when adjusted for age, race, gender and other comorbid conditions. Mortality is however highest in the older age group and diabetic patients [15].

Majority of patients with CRF are between the ages of 20-55years. Since most of the patients cannot afford treatment, many of them are still being managed conservatively, which include renal diet in form of low protein, low potassium/sodium diet. However, this approach has not been very effective in our patients as most of them come late to the hospital. Dietary treatment in form of protein restriction and supplement with ketoanalogues has been shown to be helpful in early stage of the disease [25]. The modalities of treatment e.g dialysis and transplantation have become prohibitive in cost and conservative

estimate may be more than 1.5 million naira (about $12,000) per year for dialysis alone in Nigeria. As if that is not enough, dialysis facilities remain inadequate, few machines are available per center and software spare parts are not regularly available and vascular assess for chronic dialysis is costly. Renal transplantation can now be done in Nigeria. It may cost between two and three million naira to get transplanted, yet the patient will have to provide the donor. Donor sourcing is a big problem even in advanced countries. In one study in Ife, only 47.3% of a cohort of hospital workers was willing to donate their kidneys and 4% of them wanted some financial reward for this [26]. Furthermore, to maintain the donor kidney, the patient should be able to procure immunosupressants, this has contributed to the high cost of post transplant maintenance of the patients, which may cost as much as N120, 000 per month in the early post transplant period in Nigeria. The consequence of the association between kidney and hypertension on the patient and the family, the national economy and the society at large is therefore evidently clear and considerable. Experience in Nigeria has shown that a large number of patients with CRF can neither afford dialysis nor transplantation [27]. There were very few survivors per year and the average mortality figure may be as high as 87% in 3 months [27] (Table 2). This gloomy outlook in Nigeria is largely due to lack of fund for treatment on the part of the patients, and occasionally lack of regular supplies of dialysis software. The above appraisal highlights the dimension of the problems posed by the association of kidney and hypertension and the difficulty in managing end stage renal failure especially in developing countries like Nigeria. It is therefore necessary to make a clarion call for preventive nephrology in developing nations in general and in Nigeria in particular; this may help in reducing the burden of the disease and the number of those who will require dialysis in future.

Table 2: Mortality and dropout rate of CRF patients' dialyzed using hemodialysis in Ibadan

Yrs	Patients	Death	Lost to follow-up	Alive	Mortality %	Dropout rate %
1990	8	4	1	3	-	-
1991	47	30	11	6	64	23
1992	55	33	15	8	60	27
1993	42	28	12	2	67	29
1994	24	15	7	1	63	29
1995	40	20	13	7	50	33
Total	216	130	59	27	60	27

In conclusion, the association between the kidney and hypertension has been explained. The prevalence of hypertension is high globally and the incidence of renal disease is also increasing dramatically. It has become a significant public health problem both economically and medically. The morbidity and mortality associated with the modalities of treatment in our environment i.e dialysis and transplantation are substantial and outcomes for now are still not encouraging. Hypertension is implicated in the development of end stage renal disease and better control of it should be an important goal in primary care medical practice.

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