

HYPERTENSIVE NEPHROSCLEROSIS AND ITS PREVENTION

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Abstract : With increasing life expectancy, hypertension has emerged as an important worldwide public health problem. It has become a leading cause of chronic kidney disease and increases risk of CKD progression and cardiovascular disease risk. JNC VII Report defines normal blood pressure as systolic and diastolic readings of <120 AND <80 mm of Hg respectively. The kidneys play a key role in the regulation of fluid volume and vascular tone. The histological lesions of hypertension-induced kidney damage are non-specific, the earliest and most frequent lesion in longstanding hypertensives is segmental hyalinization of interlobular arteries and afferent arterioles, glomerular and tubular compartments are affected secondarily. Therapeutic interventions aimed at reducing kidney damage in hypertension are aimed at reduction of systemic blood pressure, reduction of pressure transmission to the renal microvasculature and modification of local molecular pathways to attenuate tissue injury. Management starts with lifestyle modification and then to drug therapy. The choice of drug is influenced by the presence of concomitant medical conditions. Diuretics and drugs acting at the renin-angiotensin pathway are the preferred agents. The latter are especially useful in proteinuric individuals. Statins are important adjuncts in those with high cholesterol. In future, strategies that either directly halt the molecular processes leading to hypertensive renal damage or allow reversal of established renal damage may become available.

INTRODUCTION

In this era of chronic diseases, hypertension has emerged as an important worldwide public health problem. As the life expectancy increases, an increasing proportion of the ageing population is developing hypertension; an individual who is normotensive even at the age of 55, carries a 90% lifetime risk of developing hypertension.¹ Hypertension prevalence depends on the racial and ethnic population mix in different geographic areas as well as the criteria used to define it. This condition is traditionally classified into 'essential' and 'secondary' categories. The term 'essential' was coined with the understanding that an increase in blood pressure is a necessary phenomenon required to maintain normal organ perfusion as the arteries stiffen with age, but has largely been discarded in favor of 'primary' or 'idiopathic' hypertension. The frequency of secondary forms of hypertension depends on the nature of population studied and extensiveness of the evaluation, and varies from 6% in general population to 35% in referral centers².

EPIDEMIOLOGY

BP readings in the general population fall in a Gaussian distribution, but are skewed towards the higher end, making it difficult to choose a single value that would denote the cut off between normotension and hypertension. The definition and grading of hypertension has evolved over the last 25 years; the latest criteria have been proposed in the Seventh Report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)³. According to this report, normal blood pressure is defined by systolic and diastolic readings of <120 AND <80 mm of Hg respectively. Stage I and II hypertension are defined as SBP of 140-159 and/or DBP 90-99 and SBP e'' 160 and/or DBP e'' 100 respectively. A new category of "prehypertension", defined as a SBP of 120-139 OR DBP 80-89 mm of Hg, was introduced in this report.

The third National Health and Nutrition Examination Survey carried out in the United States between 1988 and 1991 used the JNC V criteria, and categorized 24% of the adult population as having hypertension⁴. The prevalence was 4% amongst the 18-34 year olds, but increased to 58.5% in the age group 65-74 years⁵. African-Americans exhibit a 50-75% higher prevalence and have the highest incidence of hypertension-related ESRD⁶. The 1998 Health Survey in England defined high BP as SBP e''140 and DBP e''90, or antihypertensive drug use, and found the prevalence to be

40.8% for men and 32.9% for women⁷. Indian urban population studies of the mid-1980s used older WHO guidelines for diagnosis (BP e''160 and/or 95 mmHg) and reported hypertension prevalence of 1.2-4.0%⁸. Subsequent studies have reported a steady increase in prevalence: from 5% to 12-15%⁹. Prevalence is lower in the rural Indian population, although there has been a steady increase over time here as well. The most recent studies using revised criteria (BP e''140 and/or 90 mmHg) have shown a prevalence of 15-40% among urban adults¹⁰.

Hypertension is a leading cause of end-stage kidney disease (ESRD) in the west. Hypertension was listed as the cause in 27% of incident ESRD patients in the United States in 2000, second only to diabetes mellitus¹¹. However, the basis for making this diagnosis is not uniform in all reports. In a prospective study of 56 Caucasian patients, the clinical diagnosis of hypertensive nephrosclerosis could be confirmed on renal biopsy in only 48%, whereas 35% showed atheromatous vascular disease¹². Hypertension was listed as the primary cause of chronic kidney disease (CKD) in 14.5% of cases in the Indian CKD Registry (Rajapurkar M, for Indian CKD Registry Group).

On the other hand, a major contribution of hypertension in the progression of all types of chronic kidney diseases is not doubted. Both SBP and DBP were shown to be strong independent predictors of ESRD in the cohort of 332,544 men followed up for 16 years for the Multiple Risk Factor Intervention Trial. In comparison to the normotensive (BP d''120/80), those with a SBP e'' 210 mm Hg or DBP e''120 mm Hg exhibited a 22-fold increased risk of developing ESRD¹³. Hypertension is also an important cardiovascular disease risk predictor. Starting at 115/75 mm Hg, the CVD risk doubles with each increment of 20/10 mm Hg³.

KIDNEYS AND BLOOD PRESSURE

The kidneys play a key role in the regulation of fluid volume and vascular tone. The intravascular volume control involves regulation of water and sodium excretion and vessel tone depends upon secretion of vasoactive substances by the kidneys. An elevation in renal perfusion pressure results in an increased excretion of sodium and water, the so called "pressure natriuresis/diuresis". According to Guyton, pressure natriuresis promotes the excretion of sodium and water until blood volume is diminished sufficiently to return blood pressure back to normal range¹⁴. Many compounds, including rennin, vasopressin, atrial natriuretic peptide and angiotensin II play an important role in this pressure natriuresis. The renin-angiotensin system is a powerful regulator of arterial pressure, sodium balance and intraglomerular pressure¹⁵.

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EFFECTS OF HYPERTENSION ON KIDNEYS

The adverse effects of hypertension on kidneys are determined by the level of systemic blood pressure as well as the abruptness with which this pressure load is transmitted to the renal vascular bed. Increase in systemic blood pressure is normally followed by proportionate autoregulatory vasoconstriction of preglomerular arterioles so that the high pressure is not transmitted to the renal microvasculature, and the renal blood flow and glomerular hydrostatic pressure are maintained at a constant level^{16,17}. The histological lesions of hypertension-induced kidney damage are non-specific, and do not allow differentiation between the different causes of high blood pressure. The earliest and most frequent light microscopic lesion in longstanding hypertensives is segmental hyalinization of interlobular arteries and afferent arterioles. Media is affected preferentially, and exhibits a diminished number of smooth muscle cell nuclei¹⁸. Immunofluorescence and electron microscopy reveal deposits of plasma constituents such as IgM and complement components (C1q, C3) within the hyalinized areas¹⁹. Similar lesions are noted in animal models of chronic hypertension. The glomerular and tubular compartments are affected secondarily. Some patients, especially those with pronounced narrowing of the interlobular arteries and afferent arterioles, may exhibit prominent ischemic collapse of the glomerular tuft. These lesions have been described under the rubric of "benign nephrosclerosis". The lack of a specific phenotype makes it difficult to quantitate the contribution of hypertension to progressive renal diseases of other etiologies, as the classical vascular pathology of hypertension is usually obscured by lesions of underlying disease. An accelerated glomerulosclerosis superimposed on the intrinsic phenotype is often the only finding^{20,21}.

A different histological picture dominates patients in whom the blood pressure rise is sudden and exceeds the autoregulatory limits. Dubbed "malignant nephrosclerosis", these lesions predominantly affect the intimal space of small sized blood vessels, particularly the interlobular arteries and afferent arterioles²². The subendothelial compartment gets filled up with plasma and cellular blood constituents. This is often accompanied by fibrinoid necrosis of the media. The intimal process dominates, however, and leads to severe narrowing of the vascular lumen. Over time, myointimal cells make their appearance, followed by collagen deposition. Hyperplasia of the juxta-glomerular epithelioid cells, ischemic collapse of the glomerular tufts, tubular atrophy, and interstitial fibrosis usually follow²³. At one time, it was believed that decline in glomerular filtration rate occurred only in those with malignant nephrosclerosis, but this view is now largely discounted.

PATIENT EVALUATION

The main objectives³ of evaluation of patients with hypertension are: 1. lifestyle assessment and identification of other cardio-vascular risk factors; 2. investigation for the presence of secondary causes of hypertension; and 3. evaluation of target-organ damage (Table 1). This requires a proper medical history, physical examination, laboratory tests, and specific diagnostic procedures.

Ambulatory BP Monitoring

In contrast to office measurements, which are intermittent and taken at fixed time points, twenty-four-hour ambulatory blood pressure monitoring allows periodic (half hourly or hourly) documentation of blood pressure during normal daily activity and provides an idea of "blood pressure load"²⁴. Ambulatory monitoring is useful for evaluation of 'white-coat' and drug resistant hypertension, and in those developing hypotensive symptoms with medications, episodic hypertension, or autonomic dysfunction. Ambulatory BP values are usually lower than clinic readings. Hypertensive individuals have a mean BP >135/85 and >120/75 mm Hg during daytime and sleep respectively²⁵. There is some suggestion that ambulatory BP records correlate better with target-organ injury than office measurements^{26,28}. Another utility of ambulatory BP monitoring is

evaluation of the extent of diurnal variations in BP. Normally, BP decreases by 10% to 20% during sleep; individuals who do not show this decrease (non-dippers) are at increased risk for cardiovascular events²⁷. The proportion of non-dippers increases as renal function deteriorates²⁴.

Table 1: Evaluation of a patient with hypertension*

Major Risk Factors:
Cigarette smoking
Obesity (BMI ≥ 30)
Physical inactivity
Dyslipidemia
Diabetes mellitus
Microalbuminuria or estimated GFR <60 mL/min
Family history of premature cardiovascular disease (men <55 years or women <65 years)
Identifiable Causes of Hypertension:
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing syndrome
Pheochromocytoma/Coarctation of the aorta
Thyroid or parathyroid disease
Target-Organ Damage:
Left ventricular hypertrophy/angina or prior myocardial infarction, heart failure, stroke or transient ischemic attack, chronic kidney disease, peripheral arterial disease/retinopathy *modified from JNC 7 recommendations (reference 3)

MICROALBUMINURIA AND HYPERTENSION

Excretion of increased amounts of albumin in urine, yet below the threshold value for positivity by routine dipstick testing, is a feature of many diseases including hypertension. Antibody-based assays (radioimmunoassay, enzyme immunoassay and nephelometry or turbidimetry) are required to detect such small amounts of albumin. Termed microalbuminuria, this corresponds to an albumin excretion rate of approximately 20-200 μ g/min or 30-300 mg/day. Commercial test strips allow quick semi-quantitative screening²⁹. Use of a timed 24-h urine sample is considered as 'gold standard' but the urine albumin-creatinine ratio on random urine samples is an acceptable alternative; a ratio of 30-300 μ g albumin/mg creatinine indicates microalbuminuria³⁰. Several studies have shown a strong influence of microalbuminuria in predicting cardiovascular risk in diabetic and non-diabetic hypertensive subjects^{31,32}. It has been interpreted as an indicator of generalized inflammatory process or endothelial dysfunction in several conditions including diabetes, essential hypertension, obesity and metabolic syndrome. Some recent studies, most notable of which is the PREVEND trial conducted in the Dutch city of Groningen, have shown that presence of even smaller quantities (<30 mg/day) of albumin or albumin fragments may indicate increased cardiovascular risk³³. Such small quantities can be detected only by HPLC. This finding needs confirmation in prospective studies.

PREVENTION OF HYPERTENSIVE RENAL DISEASE

Therapeutic interventions aimed at reducing kidney damage in hypertension can be tailored to fulfill one or more of the following three broad strategies: 1) reduction of systemic blood pressure load; 2) reduction of pressure transmission to the renal microvasculature; and 3) modification of local molecular pathways that mediate eventual tissue injury.

Out of these three approaches, the most successful one is the reduction of systemic blood pressure by non-pharmacological and pharmacological means. According to current standards, the acceptable blood pressure goal for target organ protection is <140/90 mmHg; reduced further to <125-130/75-80 mmHg in those with diabetes or chronic kidney disease³. The algorithm for the treatment of hypertension as proposed by JNC 7 is shown in Figure 1. The first step in mild-to-moderate hypertension should always be *life-style modification*; *drug therapy* should be considered only if these fail or when the hypertension is severe.

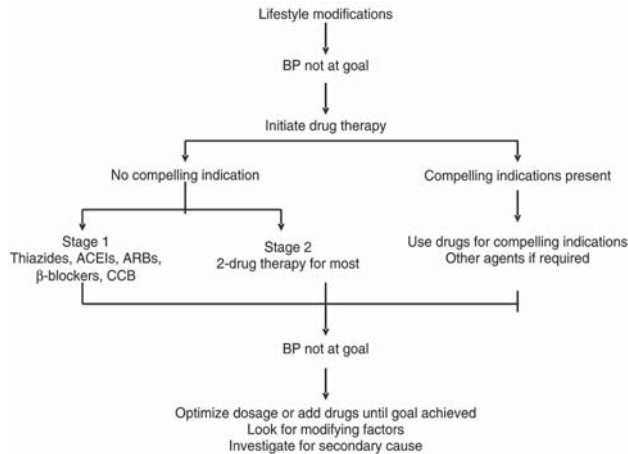


Figure 1: Algorithm for treatment of hypertension (modified from JNC 7³)

LIFESTYLE MODIFICATIONS (TABLE 2)

Healthy lifestyle is critical for the prevention management of hypertension. Major lifestyle modifications shown to lower BP include weight reduction in the overweight^{34,35}, increased physical activity³⁶, cessation of smoking and moderation of alcohol consumption³⁷. JNC 7 also recommends adoption of diet rich in potassium and calcium and low in sodium, as described in the Dietary Approaches to Stop Hypertension (DASH) study³⁸. Lifestyle modifications not only decrease blood pressure by itself but also enhances efficacy of antihypertensive drugs.

Prehypertension has not been considered a disease in JNC 7, but identifies individuals at high risk of developing hypertension. All prehypertensives should be strongly advised to practice lifestyle modification. Those with diabetes or CKD are candidates for appropriate drug therapy if a trial of lifestyle modification fails to reduce their BP to 130/80 mmHg or less.

Table 2: Life-style modifications in hypertension

Modification	Recommendation
Weight reduction	Maintain Body mass Index between 18.5-24.9 mg/m ²
Diet	1. Adopt a diet rich in fruits, vegetables and low-fat dairy products with reduced content of saturated and total fat. 2. Reduce dietary sodium intake to ≤ 100 mEq/L (6 gm of sodium chloride or 2.4 gm of sodium)
Physical activity	Regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)
Alcohol consumption	Limit consumption to no more than 2 drinks per day in men and no more than 1 drink in women and lighter-weighted persons
Smoking	Stop smoking completely

DRUG THERAPY

Life-style modifications alone are sufficient to bring the BP down to goal only in a minority of individuals, and most require drug therapy for adequate control. Given below is the list of drugs which are used for blood pressure reduction. Multiple drugs are frequently required to achieve the target.

1. Diuretics (thiazides and loop diuretics)
2. Angiotensin converting enzyme inhibitors (ACEI)
3. Angiotensin receptor blockers (ARB)
4. b-adrenergic blockers
5. a-adrenergic blockers
6. Calcium-channel blockers (CCB), especially dihydropyridines
7. Centrally acting drugs (e.g. clonidine, methyldopa)
8. Vasodilators (e.g. minoxidil, hydralazine)

In this era of evidence-based medicine, there is little data on the differential renoprotective effects of antihypertensive agents in management of uncomplicated hypertension. The primary outcome measures in most antihypertensive clinical trials have been heart failure, ischemic heart disease or stroke. Most of the available data on renoprotection has come from studies on patients with pre-existing chronic kidney disease of diabetic and nondiabetic etiologies.

Table 3: Considerations for individualization of anti-hypertensive therapy

Indication	Initial Therapy	Second line therapy	Notes/Cautions
DM with nephropathy	ACEI/ARB	Add thiazide, β-blockers, LA-CCB, ACE/ARB combo	Cardioselective β-blockers
DM without nephropathy	ACEI/ARB or thiazide	Combo 1st line Rx or β-blockers, LA-CCB	If serum creat > 1.8 mg/dL, use loop diuretic for volume control
Angina	β-blockers + strongly consider ACEI	LA-CCB	Avoid short acting nifedipine
Prior MI	β-blockers + ACEI	Combine additional Rx	
CHF	β-blockers + ACEI + spironolactone (ARB if ACEI intolerant)	Hydralazine /nitrates thiazide or loop diuretics as additive therapy	Avoid non DHP-CCB (diltiazem, verapamil)
Prior CVA or TIA	ACEI/diuretic combination		BP reduction ↓ recurrent events
Renal Disease	ACEI/diuretic as additive Rx	ARB if ACEI intolerant Combo other agents	Avoid ACEI if bilateral Renal artery stenosis
LVH	ACEI, ARBs, DHP-CCB, thiazide, β-blockers < 55 yr		Avoid hydralazine and minoxidil

Several guidelines on managing hypertension have been published, four in 2003 alone. While containing large measures of agreement, these guidelines are not unanimous in their recommendation of the initial antihypertensive drug and the method of subsequent management; whether drugs should be added (stepped-care) or exchanged (sequential design). JNC 7, chiefly on the basis of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)³⁹, recommends use of diuretics, particularly thiazides, as the first line agent. This trial compared chlorthalidone, lisinopril, amlodipin and doxazosin in about 45,000 individuals (32% African-Americans), all above the age of 55 years. Compared to diuretic-treated individuals, those treated with doxazosin⁴⁰ and amlodipin had higher rates of heart failure, and lisinopril-treated individuals showed increased frequency of heart failure as well as stroke³⁹. Other smaller trials like Perindopril Protection against Recurrent Stroke Study (PROGRESS)⁴¹ have shown similar findings. The lower cost of thiazides makes them particularly attractive as the initial agents. Diuretics also enhance the antihypertensive efficacy of multi-drug regimens; and help achieve BP control in cases of resistant hypertension. According to JNC 7, hypertension can only be defined as drug-resistant when diuretics have been tried and found ineffective as a part of combination therapy³.

The ALLHAT trial, however, has been criticized on several counts,

specifically the generalizability of findings in a selected patient population, and the assumption that drugs added later (in the second or third step) are not important in outcome analysis. The Second Australian National Blood Pressure Trial⁴² reported better outcomes in white elderly men with a regimen that began with an ACE inhibitor compared with one starting with a diuretic. Most studies that have shown favorable effects of ACE-inhibitors have used them in larger dosage than those used in clinical practice (e⁺ 10 mg/d of ramipril, 20-40 mg/d of benazepril or e⁺ 8 mg/d of perindopril). It has been suggested that different treatment approaches may be required for managing blood pressure in different population groups. In a study of single-drug therapy, it was found that young white individuals responded better on ACE inhibitors and b-blockers, but poorly to diuretics whereas the BP in older whites responded best to CCBs. Blacks of all ages responded poorly to ACE inhibitors⁴³.

Many studies, including Study of Left Ventricular Dysfunction (SOLVD)⁴⁴, Survival and Ventricular Enlargement (SAVE)⁴⁵ and Heart Outcomes Prevention Evaluation (HOPE)⁴⁶ have demonstrated that ACEIs reduce cardiovascular and stroke-related morbidity and mortality. Several trials, like ACE Inhibition in Progressive Renal Insufficiency (AIPRI)⁴⁷, ACE Inhibitors in Diabetic Nephropathy⁴⁸, RENAAL⁴⁹ and IDNT⁵⁰ have confirmed the renoprotective effect of ACEIs and/or ARBs in those with CKD of both diabetic and non-diabetic etiologies. The African American Study of kidney disease and hypertension (AASK)⁵¹ showed ACEI to be more effective than b-blockers or dihydropyridine CCBs in slowing the decline in GFR in patients with non-diabetic kidney disease, even in patients who did not have significant proteinuria. JNC 7 and Kidney Disease Quality Outcome Initiative (K-DOQI)⁵² recommend using these drugs preferentially in those with heart failure, diabetes or chronic kidney disease (Table 3), especially in those with significant proteinuria (> 1g/d). Because of their physiological differential effects on the afferent and efferent arterioles, a moderate acute decline in glomerular filtration rate (GFR), reflected by up to 30-35% increase in serum creatinine above baseline is expected after initiating treatment with ACEIs or ARBs. This should not be a reason to withhold or stop treatment. A watch must be kept for the first-dose effect and later development of hyperkalemia, especially in those receiving potassium-sparing diuretics or substantially reduced GFR.

Centrally acting drugs and vasodilators are usually used in combination with other drugs in cases of refractory or resistant hypertension and seldom on their own as first line agents. A notable exception has been the Kidney Help Rural Trust project⁵³, in which cheap drugs like reserpine have been successfully used for bringing down the blood pressure. However, their efficacy in target organ protection has not been examined.

In many individuals, complete normalization of systemic blood pressure is not sufficient in halting progression of kidney disease completely. Whether other renoprotective approaches would be useful in adding to the effect of conventional antihypertensive therapy remains to be seen. Mitigating renal damage by reducing intrarenal transmission of systemic blood pressure can be theoretically achieved by protein restriction, but benefit of this approach is only modest and discernible in only those with more advanced renal disease⁵⁴. Similarly it may become possible in future to independently modulate the downstream molecular mediators of tissue injury.

The place of drugs that do not reduce the blood pressure in target organ protection due to hypertension is being explored. Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm study (ASCOT-LLA)⁵⁵ showed that a group of hypertensive patients that received 10 mg/day of atorvastatin had a 36% relative risk reduction in the primary study end point of combined nonfatal myocardial infarction plus fatal coronary heart disease. In addition, the secondary end points of nonfatal and fatal stroke (27% relative risk reduction), total coronary events (29%), and total cardiovascular events and related procedures (21%) were also significantly affected. There was a 13% reduction in all-cause mortality, which was not significant. The ALLHAT-LLT⁵⁶ however showed that addition of pravastatin does not have any added benefit then the usual care in moderately hypercholesterolemic hypertensive patients. There is some

evidence that high doses of atorvastatin may, by itself, reduce BP levels, especially systolic BP.

CONCLUSIONS

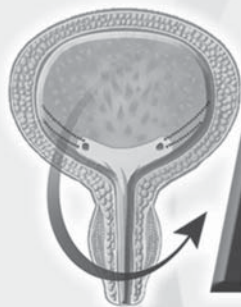
Hypertension is a common clinical and public health problem. It is an important cause of ESRD, and plays a major role in worsening the progression of chronic kidney disease due to other causes. There is insufficient data to determine optimum renoprotective strategies for those with uncomplicated hypertension. The current recommendations include adequate BP control by combination of life-style modifications and one or more drugs, especially diuretics and drugs acting on renin-angiotensin axis. Statins are important adjuncts in those with high cholesterol. In future, strategies that either directly halt the molecular processes leading to hypertensive renal damage or allow reversal of established renal damage may become available.

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