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Hypertension and Type 2 Diabetes Mellitus
Metabolic Interface & Vascular Biology

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Abstract

The association of essential hypertension and type 2 diabetes mellitus (T2DM) is well recognized. This combination of co-morbidities, with the constellation of common risk factors, results in considerable disease burden with consequent loss of quality adjusted life years (QUALY). To the generally known mechanisms, particularly insulin resistance, underlying obesity, T2DM, hypertension and cardiovascular disease, has now been added the contributory role of low-grade inflammatory process. New insights into endocrine-metabolic interactions with vascular biology have highlighted the role of adiponectin and renin-angiotensin-aldosterone system. While adiponectin acts as an integrator of metabolic and inflammatory signals, its low levels are associated with obesity, T2DM and coronary heart disease. There is also negative correlation between circulating level of adiponectin and markers of inflammation including CRP, PAI-1 and tissue plasminogen activator (tPA). In contrast to anti-inflammatory role of adiponectin, angiotensin II is proinflammatory resulting in upregulation of inflammatory transcriptor factors such as NF-kappa B (NF-κB). These in turn lead to endothelial dysfunction and vascular injury. Advances in the understanding of molecular mechanisms may lead to rational development of new therapeutic interventions.

Key Words : Quality adjusted life years, inflammatory transciptor factors, endothelial dysfunction, vascular injury

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Introduction

The association between hypertension and T2DM is well recognized. More than 80% of patients with T2DM develop hypertension and approximately 20% of patients with hypertension develop diabetes. Combined together, these account for a large proportion of cardiovascular morbidity and mortality. Whilo tho pathophysiology of medium and large vessel diseases is multifactorial, there is strong suggestive evidence that metabolic profile along with low-grade inflammatory process constitute the base and basis of pathogenic mechanism(s).

Metabolic Interface

Subjects with hypertension (HT) have higher risk of developing insulin resistance. Systolic blood pressure is a significant predictor of subsequent development of T2DM irrespective of age and gender. In our own study at the AIIMS, New Delhi wherein 38 young healthy non-obese (mean BMI ~ 22.74) normotensive offspring of hypertensive parents were investigated, higher levels of insulin *both* in the fasting state and during oral GTT were observed in 23 (62%) of the subjects (1). Hyperinsulinemia indicates insulin resistance as was well documented in earlier studies. Reaven has suggested that adiposity and physical fitness each account for approximately 25% of the variability in insulin sensitivity, with genetic factors responsible for an additional 50% of the variation (2). Our data of hyperinsulinemia in non-obese normotensive offspring of hypertensive parents supports the partially genetic basis of insulin resistance.

Subjects with HT, newly diagnosed and prior to the administration of any antihypertensive treatment, showed during OGTT a high AUC glucose, alongwith significant hyperinsulinemia, suggestive of insulin resistance. Indeed, there seems to be a correlation between mean BP (mmHg) and insulin sensitivity (ml/min/Kg): Insulin sensitivity is inversely related to severity of hypertension. Those subjects with more severe hypertension are more likely to have greater insulin resistance (3).

Equally significant is the observation that level of blood glucose at any point in time may be predictive of developing hypertension several years later. In a landmark study of public health importance, blood glucose concentration one hour after a glucose load, blood pressure and body weight were measured in a cohort of men at 5-7 years interval in 1968, 1974, 1979 and 1986. Regression

analysis showed that the higher the blood glucose concentration after a glucose load in 1968, the higher the blood pressure during the following years. Those men between the second and third tertiles of blood glucose concentration in 1968 had a significantly higher risk of developing hypertension (odds ratio 1.71, 95% confidence interval 1.05 to 2.77) compared with those below the first tertile (4).

The possibility that obesity, especially visceral fat, may provide the link between diabetes mellitus and hypertension is strongly supported by available data. While the association of visceral adipose tissue (VAT) with glucose intolerance, dyslipidemia and hypertension is well recognized and constitutes the phenotype of metabolic syndrome, there is strong evidence for an independent association of increase in VAT with hypertension and insulin resistance.

Studies in children show that rise in blood pressure is associated with hyperinsulinemia and VAT excess (5). Likewise, in hypertensive women with central adiposity, accumulation of fat in abdominal viscera is associated with insulin resistance and also with higher levels of blood pressure (6). In a recent study of 13 nondiabetic men with newly detected untreated essential hypertension, VAT and subcutaneous fat were estimated using multiscan MRI. Age and BMI-matched normotensive subjects were taken as controls. In both groups, insulin secretion was measured during oral glucose tolerance test, and dynamics of β-cell function were calculated by mathematic modeling. The study confirmed that abdominal VAT, insulin resistance, and blood pressure were quantitatively interrelated. While VAT excess was quantitatively related to both the height of blood pressure and severity of insulin resistance, there was no demonstrable impact on the dynamics of β-cell function (3).

In view of the association of insulin resistance, hyperinsulinemia and dyslipidemia, the role of lipids in pathogenesis of cardiovascular disease needs consideration. Small, dense LDLs, and excess triglyceride-rich remnants, which are highly atherogenic, are increased in the insulin-resistant state (7). There is also an overproduction of very low-density lipoproteins (VLDLs) which can accelerate the atherosclerotic process in several ways, including direct effect on the metabolism and growth of endothelial cells. Low HDLs, associated with insulin resistance, are unable to reduce the inhibitory effect of LDL on endothelium-mediated vasodilation. Finally, hypercholes-

terolemia increases the expression of endothelial adhesion molecules. Visceral adiposity, insulin resistance, and hypertension constitute the metabolic interface underlying cardiovascular morbidity and mortality associated with type 2 diabetes mellitus (T2DM) and essential hypertension.

Insulin Resistance, Vascular Biology, and Cardiovascular Disorders

It took nearly sixty years following the discovery of insulin to convincingly demonstrate its direct effects on the vasculature in dogs, and another decade to establish similar vascular effects in humans (8). Insulin, in concentration at the high physiological range, as observed in the postprandial phase, produces a nearly two-fold increase in skeletal muscle blood flow in non-obese insulin-sensitive subjects. The vasodilatory effect of insulin occurs within about 30 minutes of administration coinciding temporally with its effects on glucose uptake in the muscle. The mechanism underlying the vasodilatory effect of insulin is through the release of endothelium derived nitric oxide (eNO). Such release of eNO is mediated through signaling pathways involving tyrosine kinase, PI3K, and Akt, downstream from the insulin receptor (9). Thus the metabolic and vascular actions of insulin share common signaling pathways.

In addition to enhancing blood flow in the skeletal muscle, insulin also augments stroke volume, increases heart rate, as well as cardiac output (10). Furthermore, insulin causes antinatriuresis, antikaliuresis, and antiuricosuria in healthy human volunteers. Insulin also modulates the response to vasopressor hormones i.e. norepinephrine, vasopressin, and angiotensin II both at the level of vascular endothelium, as well as at vascular smooth muscle cell *independent* of the endothelium (11). Taken together, there is a net effect of insulin on blood pressure. Thus, any imbalance between the vasodilatory effects of insulin and the opposite effects of other vasoconstrictor hormones, may result in elevation of blood pressure and accelerated development of macrovascular disease.

Obesity causes a shift to the left in the vasodilatory response to insulin. The medium effective dose (ED_{50}) for insulin to increase leg blood flow in the obese was approximately four times (~ 160 μU/ml) that in the lean subjects (44 μU/ml). Subjects with T2 diabetes showed a more pronounced impairment of insulin-mediated vasodilation : only supraphysiologic

hyperinsulinemia (~ 2000 μU/ml) resulted in a 33% increase in blood flow (12). Similar observations were made when subjects with essential hypertension were studied. It was surmised that the impaired insulin-induced vasodilation as observed in obesity, type 2 diabetes and hypertension was a result of impaired production of NO.

A sound conceptual framework for the understanding of molecular linkage between insulin resistance, hyperinsulinemia, and increase risk of cardiovascular diseases or atherosclerosis in T2DM, has been provided in recent studies. Insulin receptors have been demonstrated on the vascular cells; these receptors are identical with those on the nonvascular cells with respect of structure, affinity, binding kinetics, capacity for tyrosine phosphorylation, and activation of tyrosine kinase (13). As in other cells, insulin binding with its receptors on vascular cells results in the activation of two separate signal transduction pathways: (i) the phosphatidylinositol (PI) 3-kinase pathway; and (ii) the Ras-mitogen-activated protein (MAP) kinase pathway. Under physiological concentrations of insulin, the vascular effects are mainly mediated by PI3-kinase pathway. However, in insulin resistant states with resultant hyperinsulinemia and persistent elevation of plasma insulin concentrations, MAP-K pathway is continuously activated, leading to proliferation and migration of smooth muscle cells in aorta and large blood vessels, alongwith a marked increase in the synthesis of extracellular matrix proteins in the arterial wall (14). In addition to these direct effects, insulin may also enhance the mitogenic effect of more potent growth factors, such as platelet-derived growth factor, and insulin-like growth factors.

It has already been mentioned that PI3-kinase pathway is involved in the release of endothelium derived nitric oxide, and that the vasodilatory effects of insulin are considerably impaired in insulin-resistant states. The role and place of PI3-kinase and ras-AMP kinase pathways in vascular endothelial cells can now be succinctly conceptualised. At physiological concentrations, insulin-mediated vasodilation is mainly through PI3-kinase activation, leading to NO production (acute effect) and enhanced gene expression of eNOS (delayed effect). These effects are antiatherogenic. In contrast, insulin-mediated effects through ras-MAP kinase pathway, resulting in vascular smooth muscle cell growth, proliferation and

migration, along with stimulation of extracellular matrix production, are atherogenic requiring persistently elevated concentrations of insulin as encountered in insulin-resistant states. Thus, accelerated atherosclerosis in T2DM is due to a combined effect of impaired insulin effects mediated by PI3-kinase pathway *without* the inhibition of insulin effects mediated by ras-MAP kinase pathway. The differential effects of insulin resistance on the PI3-kinase and MAP kinase-mediated signaling in human muscle, are major determinants of alteration of vascular biology in insulin resistant states such as type 2 diabetes and obesity. The subject has been recently reviewed (15).

Experimental evidence, generated in recent years, does show that mice with gene disruption of endothelial nitric oxide synthase (eNOS) (16) or neuronal nitric oxide synthase (nNOS) exhibit insulin resistance, hypertension, and dyslipidemia. Induction of iNOS by endotoxin is associated with impaired insulin-stimulated glucose uptake. In contrast, targeted disruption of iNOS protects against obesity-linked insulin resistance in muscle (17). Recent clinical studies indicate marked impairment of insulin activation of IRS-1/PI3-kinase pathway in the muscle of normal-glucose-tolerant insulin-resistant offspring of two diabetic parents. Thus, both the metabolic effects of insulin and its vasodilatory effects are linked together through IRS-1/PI3-kinase pathway and insulin resistance even at an early stage, when glucose tolerance is normal, results in impairment of both metabolism and vasodilation.

Vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) are established cardiovascular risk markers. It has also been shown that NO modulates leucocyte adhesions to the endothelium by regulating the production/release of ICAM and VCAM by endothelial and vascular smooth muscle cells. In a recent study, NOS activity in skeletal muscle of well controlled T2 diabetics, who were on diet and/or sulphonylurea therapy, was investigated under basal condition and during a 80 mU/m^2 min euglycaemic clamp. Healthy age-matched, sex matched, BMI matched, and ethnicity matched subjects served as controls. Basal and insulin-stimulated muscle NOS activity was impaired in well controlled type 2 diabetic subjects. The defect in insulin-stimulated NOS activity correlated closely with the severity of insulin resistance as assessed by measurements of insulin-stimulated glucose

disposal. In addition, there was a significant increase in plasma ICAM and VCAM concentrations, with an inverse correlation between the increased plasma ICAM and VCAM levels and the reduced muscle NOS activity (9).

Hormone-Metabolic Interactions

In addition to the key role of insulin resistance and hyperinsulinemia, recent work tends to highlight the role of leptin, adiponectin, and rennin-angiotensin system. Plasma adiponectin and leptin levels had opposite and characteristic association with adiposity, insulin resistance, and inflammation. In a recent study aimed to measure coronary artery calcium (CAC), leptin but not adiponectin showed a significant correlation with CAC (18). Furthermore, plasma leptin was positively associated with higher CAC after adjustment for age, gender, and traditional cardiovascular risk factors. Combined with HOMA-IR index (homeostasis model assessment of insulin resistance), leptin had a strong predictive value for CAC, indicating possible association with coronary artery disease. Leptin has been shown to possess prothrombotic effects as it activates human platelet aggregation and adhesion, and limits transendothelial cell diffusion (19).

In contrast, adiponectin increased the integrity of diffusion barrier formed by a monolayer of human microvascular endothelial cells. Low adiponectin levels also correlate with increased inflammatory markers. Adiponectin, which is predominantly of adipocyte origin, is low in obesity possibly due to expression of transcription factors that negatively regulate the adiponectin gene. Association of low adiponectin with visceral adiposity and the risk of T2DM is well recognized. Clinical studies provide interesting data linking the metabolic and anti-inflammatory roles of adiponectin. In a study of 77 subjects who had diabetes or were at high risk to develop diabetes, there was a significant negative correlation between circulating levels of adiponectin and CRP, PAI-1, and tissue plasminogen activator (tPA) (20). These negative associations remained significant after adjusting for gender and BMI. This study reinforces earlier observation regarding the protective role of adiponectin against inflammation and endothelial dysfunction, and provides evidence of its negative association with tPA, which is known to play a role in impaired fibrinolysis. A similar study in women with prior gestational diabetes mellitus (pGDM) who are known to be at higher risk of

developing T2DM and associated cardiovascular complications, showed that plasma adiponectin was significantly lower in pGDM as compared to women with normal glucose tolerance during pregnancy. The differences remained statistically significant even after adjustment for body fat mass. Equally significant were the differences in the levels of PAI-1 and ultrasensitive CRP which were higher in the pGDM group. It was concluded that lower plasma adiponectin concentrations characterize women with previous GDM independently of the prevailing glucose tolerance, insulin sensitivity or the degree of obesity and are associated with subclinical inflammation and atherogenic parameters (21).

In a recent study of 3640 male nondiabetic subjects aged 60-79 years, there was a significant negative correlation between serum adiponectin, obesity, insulin resistance, markers of inflammation, and endothelial dysfunction (22): these factors are also known to increase the risk of T2DM. Thus the role of adiponectin as an integrator of metabolic and inflammatory signals underlying obesity, T2DM, and coronary heart disease has assumed considerable significance, both in terms of its potential as a part of preventive strategies, and also as a prototype molecule for the development of new analogues and related compounds aimed at therapeutic intervention.

Renin-angiotensin-aldosterone system (RAAS) has received considerable attention as a key mediator of cardiovascular dysfunction in diabetes, in addition to its well recognized role in the regulation of blood pressure. Angiotensin II has been shown to have direct effects on endothelial dysfunction, oxidative stress, inflammation, and adipocyte function. Of considerable relevance is the data from clinical trials demonstrating not only the antihypertensive effect of RAAS inhibitors, but also a positive effect in reducing the risk of cardiovascular and renal complications in diabetes mellitus.

The Captopril Prevention Project (CAPPP) randomized nearly 11,000 hypertensive patients to treatment with captopril or conventional antihypertensive therapy (beta blockers or thiazide diuretics). Among the 10,413 study participants who did not have DM at the time of study entry, risk for incident DM (a pre-specified secondary end point) was reduced 11% in the captopril group relative to the conventional therapy group after a mean follow-up period of 6.1 years (23).

The Heart Outcomes Prevention Evaluation (HOPE) trial compared ramipril with placebo in 9,297 patients with or at high risk for cardiovascular disease and demonstrated a 22% relative reduction in the composite end point or cardiovascular death, MI and stroke with ramipril treatment. Ramipril was also observed to prevent the development of DM, a prospectively planned secondary end point. Among the 5,720 patients without DM at study entry, 102 (3.6%) assigned to ramipril developed DM compared with 155 (5.4%) of the placebo group. The relative risk reduction in the HOPE study for incident diabetes (34%) was notably similar to that observed with metformin (31%) in the DPP study (24).

The Losartan Intervention For Endpoint Reduction (LIFE) study randomized 9,193 patients with hypertension and left ventricular hypertrophy to receive either losartan or atenolol. In this study, compared with atenolol, losartan was associated with a 25% reduction in incident DM. However, in the absence of a placebo control, it is unknown whether losartan decreased the risk of DM or atenolol increased the risk (or both) (25). Recently, a meta-analysis of 13 major trials, including the ACE-I and ARB trials described above, was performed in an attempt to evaluate the effect of inhibiting the RAAS system on incident DM. The meta-analysis found an overall decrease in the incidence of DM from 9% to 7.1% when ACE-Is or ARBs were used (26).

How does RAAS inhibition benefit metabolic and vascular outcomes? Experimental evidence suggests that ACE inhibitors (ACE-Is) as well as Angiotensin Receptor Blockers (ARB) promote recruitment and differentiation of insulin resistant preadipocytes into small insulin sensitive adipocytes (27). Thus while the overall body fat content may remain unchanged, insulin sensitivity is enhanced. A reference has already been made to insulin signaling pathway. Angiotensin II has been shown to reduce IRS-1 tyrosin phosphorylation and PI3-kinase activity via the AT_1 receptor (28). Thus ACE-Is and ARBs may inhibit angiotensin II generation and action respectively, with resultant enhancement of insulin signaling and glucose transport. Furthermore inhibition of RAAS may enhance glucose-stimulated insulin release by reducing potassium loss; preventing hypokalemia with a potassium clamp enhances glucose-stimulated β-cell insulin secretion in both healthy subjects and in patients with hypertension (29).

In addition to the endocrine-metabolic interactions described above, there is growing evidence implicating markers of low-grade inflammation as independent predictors of atherosclerotic progression, coronary heart disease (CHD), and incident T2DM (30). While ACE-Is favourably affect markers such as PAI-1, endothelin-1 and nitric oxide, ARBs have been shown to produce similar effects on VCAM-1 and CRP. Thus chronic blockade of RAAS may decrease underlying subclinical inflammatory response thereby reducing risk of incident T2DM (31) as well as CHD (32).

Perspectives

The role of hypertension, hyperlipidemia and hyperglycemia in causing arterial damage and accelerating atherosclerosis is well recognized in clinical practice. Evidence-based therapeutic management is essentially focused on normalizing these factors, in addition to incorporating appropriate life style changes and normalization of body weight.

Recent evidence points to the adverse effects of circulating peptide hormones, especially originating from adipose tissue, on constituents of blood as well as on blood vessels and resulting in an increase in the inflammatory markers in circulation along with the causation of vascular inflammation. Molecular mechanisms underlying metabolic alterations and linked with changes in vascular biology provide new insight into the understanding of the role of vascular inflammation in hypertension and T2DM. This may lead to identification of new molecular targets that may enhance the scope and range of possible therapeutic interventions.

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Evaluation of Target Organ Damage from Hypertension

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Abstract

Hypertension is not just a leading and treatable cause of cardiovascular morbidity & mortality, but also a major causative factor behind cerebrovascular, renal, retinal and peripheral vascular diseases. Cardiac failure and End Stage Renal Disease are the two major cause of death from hypertension. Complications of hypertension are usually associated with other risk factors which can exacerbate the end organ damage from hypertension. Effective, timely and aggressive treatment of hypertension can prevent or reverse these end organ damages and prevent significant morbidity and mortality in hypertensive patients. This review briefly outlines evaluation of target organ damage from hypertension & its associated risk factors.

Key Words : Hypertension, target organ damage, cardia failure, end stage renal disease, hypertensive nephropathy, hypertensive heart disease, hypertensive retinopathy

Introduction

Hypertension is a leading risk factor for coronary heart disease (CHD), heart failure, stroke, renal failure, retinopathy and peripheral vascular disease (PVD). The cutoff for defining hypertension is ideally defined as the level of arterial Blood Pressure (BP) at which benefits of intervention exceed those of inaction.

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However, a prehypertensive group was classified in the JNC 7 guidelines on hypertension as, patients with BP ranging from 120-139 mm Hg systolic (SBP) and 80-89 mm Hg diastolic (DBP), due to the increased cardiovascular risk and risk of developing hypertension. Data from observational studies involving more than a million individuals have indicated that the death from ischemic heart diseases and stroke increases progressively and linearly from SBP as low as 115 mm Hg and DBP as low as 75 mm Hg (1). The increased risk is present in all age groups ranging from 40-89 years old. For every 20 mmHg systolic and 10 mm Hg diastolic increase in BP, the mortality due to stroke and ischemic heart disease doubles (1). An increase in SBP alone has been well documented to be associated with increased risk of renal failure (RR >2.8), stroke (RR> 2.7), heart failure (RR> 1.5) , peripheral vascular disease (RR> 1.8) and coronary artery disease (RR> 1.5) (2-6). In the MRFIT study (3), those with highest SBP had highest risk of CHD mortality, a particular risk observed for those with higher SBP (>160) along with lower DBP (<70).

Hypertension is usually associated with other cardiovascular risk factors like dyslipidemia, glucose intolerance, abdominal obesity, etc., and only around 20% of the time does hypertension occur in isolation. The relationship between BP and risk of cardiovascular events is continuous, consistent and independent of other risk factors. Although the risk of death and disability associated with hypertension is increased in a statistical sense but the majority of patients with hypertension have normal longevity. This suggests that there are multiple factors operative in predicting complications from hypertension in an individual and the risks are concentrated in a subgroup rather than being randomly distributed. Thus assessment of complications from hypertension must be done with consideration of other known risk factors and timely evaluation of target organ damage. Figure 1 emphasizes the significance of silent effects of hypertension leading to overt target organ damage. This article briefly describes the approach to evaluate the target organ damage from hypertension.

Hypertensive Nephropathy

Hypertension is regarded as a cause and consequences of chronic kidney disease (CKD) which is defined in term of reduced GFR (<60ml/min/ $1.73m^2$) which corresponds to a

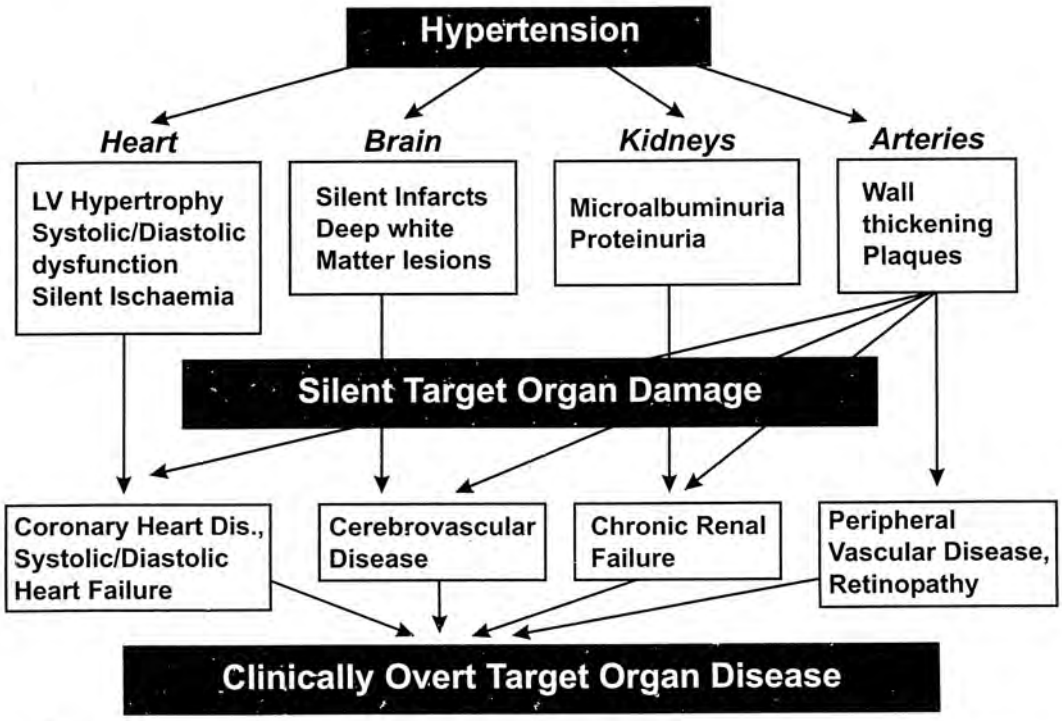


Figure 1 : Clinical significance of recognizing silent target organ damage from hypertension

creatinine level of > 1.5mg/dl in men or >1.3mg/ml in women or the presence of micro albuminuria (urine albumin >300 mg/day or 200mg/g of creatinine). Predictors for chronic kidney disease (CKD) in hypertensive patients are simple clinical parameters like age >65 years, female gender, atherogenic dyslipidemia and clinical manifestations of atherosclerosis. Black patients have an approximate eight-fold elevation in the risk of hypertension-induced end-stage renal disease (7).

The renal execretory function deteriorates with age beginning in third or fourth decade of life. This age related deterioration of glomerular filtration rate can accelerate at a rate of 4-8ml/min per year if SBP remains uncontrolled (8). Higher BP values at baseline have been significantly associated with a graded increase of the risk of end-stage renal disease. At times when antihypertensive medication had not yet become available, a large proportion of patients with essential hypertension

wound up in renal failure. This was often ascribed to the occurrence of malignant hypertension. Now with the advent of effective antihypertensive medication, malignant hypertension has become much rarer but still around 10 % of deaths caused by hypertension result from renal failure.

Patients with nephrosclerosis typically present with a long history of hypertension, slowly progressive elevations in the blood urea nitrogen (BUN) and plasma creatinine concentration and mild proteinuria. Renal damage can be assessed by looking for:

a. **Microalbuminuria:** has been defined as urine albumin >300 mg/day or 200mg/gm of creatinine. Spot urine samples may be used to calculate albumin creatinine ratio which when between 30-200mg albumin/gm creatinine denotes presence of microalbuminuria. The prevalence of microalbuinuria increases with increasing age and duration of hypertension. In a longitudinal study involving more than 4500 American Indians, microalbuminuria was associated with a significantly greater risk of developing hypertension (9). Microalbuminuria was also associated with significantly higher prevalence of LVH, coronary artery disease, Myocardial Infarction, hyperlipidemia and peripheral vascular disease (10). Measurement of microalbuminuria is a specific, cost-effective way to identify patients at higher risk, for whom additional preventive and therapeutic measures can be instituted.

b. **Proteinuria:** Protein excretion is usually mildly elevated (less than 1 g/day) in nephrosclerosis and this reflects the generally focal nature of the glomerular involvement.

c. **Microscopic Hematuria** : may occur because of glomerular lesions.

d. **Hyperuricemia:** (independent of diuretic therapy) is a relatively early finding in benign nephrosclerosis and appears to reflect the reduction in renal blood flow induced by the vascular disease.

e. **Imaging** Abdominal ultrasound, CT, MRI or other imaging modalities are not much helpful in early stages of hypertensive nephropathy but can show advanced renal damage.

Risk of renal failure in hypertension

In MRFIT study (3) a strong correlation between both SBP and DBP and end-stage renal disease was identified, independent of the association between the disease and age, race, use of medication for diabetes, history of myocardial infarction, serum cholesterol concentration and cigarette smoking. Even in patient with moderate hypertension with mean SBP 127 mm Hg and mean DBP 82 mm Hg the relative risk of renal damage is significantly increased. Interventions to prevent the disease need to emphasize the prevention and control of high as well as high-normal blood pressure (2).

Treatment

The cornerstone in management of Hypertension with CKD is optimal control of BP and inhibition of Renin Angiotensin System (RAS).

Whether hypertension is a cause or consequences of CKD, achieving an optimal blood pressure is one of the most important strategies to preserve remaining renal function. A metanalysis has shown that SBP of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression (11). Another metanlysis has shown Antihypertensive regimens that include ACE inhibitors are more effective than regimens without ACE inhibitors in slowing the progression of non diabetic renal disease (12). The beneficial effect of ACE inhibitors is mediated by factors in addition to those decreasing blood pressure and urinary protein excretion and is greater in patients with proteinuria.

Hypertensive Heart Disease

Hypertensive heart disease is a result of complex interaction between various hemodynamic and genetic factors. All these factors cause many pathological changes in heart leading to increase risk of coronary artery disease, congestive cardiac failure, stroke and sudden death. Most deaths due to hypertension result from MI or CHF. Key factors in determining the effect of hypertension on the heart are level of the pressure and time of exposure to increased pressures.

There are changes in various myocardial compositions in response to increased after load. The myocytes constitutes 75% of heart mass and 25% is interstitum that is composed of coronary vasculature, fibroblasts, macrophages and mast cells. Hypertensive heart disease causes

increase in myocyte hypertrophy and remodeling. Excess collagen deposition also causes increase in total interstitial and perivascular fibrosis which decreases ventricular systolic as well as diastolic performance.

Evaluation :

a. **Clinical:** Hypertensive patient can have dyspnea or frank heart failure secondary to diastolic dysfunction of the heart. Clinical findings in hypertensive heart disease can be enlarged heart with prominent LV impulse, accentuated aortic closure sound, frequent S4, occasional S3 or a faint murmur of aortic regurgitation.

b. **ECG:** Investigations should begin with an ECG. Various criteria are used for detection of LVH in ECG. The relative diagnostic accuracy of these methods has been tested using autopsy, radiographic, echocardiographic, and most recently MRI evaluation. The sensitivity is lower and specificity is higher for all the criteria. Repolarisation abnormalities associated with ECG findings increase the correlation with anatomical LVH.

c. **Echocardiography:** Echocardiography can be a useful tool in assessment of LVH. Accurate measurement of LV wall thickness although useful, involves a degree of subjective variation. Septal and posterior wall thickness is used for assessment of LVH but eccentric hypertrophy (characterized by chamber enlargement with normal left ventricular thickeness) is usually missed, in spite of increased LV mass.

LVH can be estimated more accurately by measuring LV mass which can be measured by calculating LV volume and multiplying it with specific gravity of myocardium (1.04g/ml). Devereux and associates derived a formula for calculating LV mass

[1.04{(LVID+PWT+IVST)3 - LVID 3} x 0.8 + 0.6] (13). Tracing of endocardial and epicardial border provides a more accurate quantification of LV mass. Three dimensional echocardiography is even more accurate to estimate LV mass. Taking MRI as a standard, inter-observer variability of measured LV mass is 37±19% with 2D echocardiography and 7±10% with 3D echocardiography (14).

Other features that can be assessed by echocardiography are

diastolic and systolic functions, valvular functions and regional wall motion abnormalities.

d. **MRI:** MRI is probably the most accurate, noninvasive method for assessment of left ventricular mass. It also gives information about myocardial structure and functions and valve diseases, but MRI may not be routinely available or feasible for evaluation of hypertension.

e. **Others:** Stress Electrocardiography has a high incidence of false positive reports in patients with LVH. Stress Myocardial Perfusion Imaging is also useful to evaluate coronary artery disease in hypertensive patients. Coronary angiography and LV angiography should be undertaken when significant coronary artery diseases is suspected.

Importance of LVH

The presence of LVH (on ECG or echocardiography) is important clinically because it is associated with increase in the incidence of systolic and diastolic heart failure, ventricular arrhythmias and sudden death following myocardial infarction and cerebrovascular events. In a prospective study, 1033 subjects over the age of 50 with essential hypertension and no previous cardiovascular events were followed for a median of three years (15). The rate of major cardiovascular events (fatal and nonfatal MI; all-cause, sudden, or cardiovascular mortality; severe heart failure; or severe renal failure requiring dialysis) was significantly higher in patients with an increased LV mass, defined as $\geq$ 125 g/m^2 body surface area (3.2 versus 1.3 per 100 patient years with normal mass). After adjustment for other risk factors, LVH was associated with an increase in cardiovascular events (relative risk 2.08). For each 39 g/m^2 increase in left ventricular mass there was a 40% increased risk of a major cardiovascular event. A report from the Framingham Heart Study examined the relationship between left ventricular mass and hypertrophy and sudden death in 3661 subjects over the age of 40 who were followed for 14 years (16). The prevalence of left ventricular hypertrophy was 22 percent and the risk factor adjusted hazard ratio for sudden death was 2.16 ($p = 0.008$). For each 50 g/m increment in left ventricular mass, the risk-factor adjusted hazard ratio for sudden death was 1.45 ($p = 0.008$) (16).

LVH is also associated with an increased risk of cerebrovascular events (stroke or transient ischemic attack), presumably because it is a marker for more severe and/or prolonged hypertension. This was illustrated by one study of 2363 hypertensive patients without cardiovascular disease who were followed for up to 14 years (17). The presence of LVH on ECG (18 percent of the group) or echocardiography (24 percent) increased the risk of a cerebrovascular event (relative risk 1.79 and 1.64, respectively). For each increase in LV mass of one standard deviation on echocardiography, the relative risk of an event was 1.31 (17).

Patients with repolarization abnormalities have more severe degree of LVH and more commonly have symptoms of left ventricular dysfunction and greater risk of cardiovascular events. In LIFE study hypertensive patients with LVH related ST-T changes were 1.8 times more likely to develop congestive cardiac failure and 2.8 times more likely to experience heart failure related death than were patients without ST-T changes (18).

Treatment and Regression of LVH:

LVH regression is associated with lower overall CVD risk. Control of BP rather than choice of drug is important. A meta analysis of fifty trials has shown that the predictors of LV mass regression are higher pretreatment LV mass, greater fall in SBP and DBP, and longer duration of treatment. The most consistent reduction in LV mass was achieved with ACEIs and least with BBs, and intermediate benefit occurred for diuretics and calcium channel blockers (19). LIFE study found that greater reduction in LV mass was with lorsatan based therapy than atenolol based therapy despite equal BP lowering effect (20).

Hypertensive Retinopathy

On the basis of the JNC criteria, the presence of retinopathy may be an indication for initiating antihypertensive treatment, even in people with stage 1 hypertension (BP:140-159/90-99 mm Hg) who have no other evidence of target-organ damage. Strong association is seen between the presence of signs of hypertensive retinopathy and elevated blood pressure. The detection of hypertensive retinopathy with the use of an ophthalmoscope has long been regarded as part of the standard evaluation of persons with hypertension. Generalized narrowing and arteriovenous nicking are markers

of vascular damage from chronic hypertension. In contrast, other signs (focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots) are related to current but not previous blood-pressure levels (21, 22). Furthermore, the observation of signs of retinopathy in people without a known history of hypertension suggests that these signs may be markers of a prehypertensive state.

A quantitative way of assessing one of the microvascular changes-generalised arteriolar narrowing in the retina - has been developed and used in population based studies (23). The photographs were digitised and the diameters of individual arterioles and venules coursing through a zone located ½ –1 disc diameter from the optic disc margin were measured with a dedicated software and summarized as an arteriole-venule ratio (AVR).

Independent associations exist between signs of hypertensive retinopathy, as defined by the findings on retinal photographs, and the risk of stroke. Some signs of retinopathy (e.g., retinal hemorrhages, microaneurysms, and cotton-wool spots) were associated with a risk of newly diagnosed clinical stroke that was two to four times as high as that for patients who did not have these signs (24). Signs of retinopathy are associated with reduced cognitive performance on standardized neuropsychological tests (25), cerebral white-matter lesions (26), and cerebral atrophy as defined on the basis of findings on magnetic resonance imaging (MRI) (27). These findings also support the concept that an assessment of specific signs, rather than the presence or absence of hypertensive retinopathy, may be important for risk stratification.

Persons with retinal arteriolar narrowing are two to six times as likely to have preexisting coronary heart disease as those without these changes (28).

Signs of hypertensive retinopathy regress with the control of blood pressure, although spontaneous resolution of these signs in the presence of high blood pressure has also been reported. It is unclear whether antihypertensive medications that are thought to have direct beneficial effects on the microvascular structure (e.g., ACE inhibitors) would reduce the damage of retinopathy beyond the reduction effected by lowered blood pressure. No data from prospective, controlled trials demonstrate that the specific reduction

of hypertensive retinopathy also reduces the morbidity and mortality associated with cardiovascular disease.

Peripheral Vascular Disease (PVD)

In addition to contributing to the pathogenesis of hypertension, blood vessels may be a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Patients with abnormal Ankle Brachial Index (ABIs) are two to four fold more likely to have a history of myocardial infarction, CCF or cerebrovascular diseases (29). Coronary calcium score and carotid intimal thickness are greater in patients with PVD. The risk of death from cardiovascular causes increases 2.5-6 fold in patients with PVD and their annual mortality is 4.3-4.9% (30).

Assessment of PVD includes clinical assessment by measuring ABI and radiologic evaluation. An ABI ratio less than 0.9 is considered abnormal. The risk of death inversely correlates with ABI (31). Radiological evaluation includes detail evaluation using ultrasound Doppler, CT scan and MRI. The gold standard is invasive angiography.

It is not clear whether antihypertensive therapy reduces progression of PVD but intensive antihypertensive therapy does reduce cardiovascular events in patients with PVD.

Cerbrovascular Diseases

Hypertension increases the risk of both ischemic and hemorrhagic stroke. The incidence of stroke rises progressively with increasing blood pressure levels, particularly SBP, in individuals >65 years. Hypertension is a cause of multiple lacunar infarcts in subcortical white matter which results in impaired cognitive function.

Doppler imaging of the carotid arteries for carotid intimal thickness gives an idea of extent of associated atherosclerosis and luminal stenosis of carotids indicates risk of future stroke. CT scan is helpful in evaluation of acute ischemic or hemorrhagic stroke. MRI studies in patients with chronic hypertension have revealed greater number of subcortical white matter lesions and micro infarcts, astrogliosis, ventricular enlargements and extracellular fluid accumulation (32). MR angiography is often performed to look for intracranial aneurysms which have a high risk of rupture in hypertensive patients.

Effective antihypertensive therapy reduces the risk of developing significant white matter changes in MRI. However white matter changes once develop, don't appear to be reversible (33). There are no comparative data available regarding whether certain classes of antihypertensives are superior to others in prevention of cognition decline. The stroke risk also decreases by control of blood pressure. No specific agents have been found to be superior in stroke prevention. In LIFE study fewer stroke occurred in losartan group than atenolol group (20). ALLHAT study has shown that stroke incidence was greater in lisinopril group than diuretics or CCB group (34). The PROGRESS trials have shown that addition of indapamide to peridopril decreases the stroke recurrence (35).

Conclusion

The message from the above discussion is that the end points from hypertensive diseases like cerebrovascular disease, CHD and hypertensive emergencies are preventable. Therapies targeted to hypertension can reverse these end organ damages if treated early and aggressively. Cardiac failure and ESRD are the two major cause of death from hypertension. Complications of hypertension are usually associated with other risk factors which can exacerbate the end organ damage from hypertension. So along with evaluation of target organ damage and control of hypertension, other risk factors should also be modified simultaneously to achieve effective benefit.

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Control and Regulation of Blood Pressure: Physiological Basis of Preventive and Therapeutic Interventions

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Key Words : Hypertension, blood pressure, autonomic control of BP, renin-angiotensin-aldosterone system, endothelialy-derived vasoregulatory substances, preventive interventions for BP, therapeutic interventions for BP

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Introduction

Hypertension is a common disease that is defined simply as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be necessary for adequate perfusion of essential organs during the early and middle 1900s, it is now identified as one of the most significant risk factors for cardiovascular morbidity and mortality worldwide (1). The risk of cardiovascular complication is as increased as BP is high and as reduced as BP is low; the risk is a continuing function of BP. Hypertension was the first quantifiable condition, identified in surveys on mortality by an American insurance company, that showed a statistical relation between the initial BP and the subsequent risk of cerebral stroke, cardiac failure, and myocardial infarction. In the 40- to 69-year old age group, a 20 mm Hg increase in systolic BP or a 10 mm Hg increase in diastolic BP is associated with more than double the risk of mortality from stroke and double the risk of mortality from myocardial infarction or other cardiovascular complications (e.g. cardiac failure, aneurysms) (2). A development of great importance to world health has been the demonstration that many of the major complications associated with hypertension are preventable by life-style modification and antihypertensive drug treatment (3). Increasing awareness and diagnosis of hypertension and improving control of BP with appropriate treatment are considered critical public health initiatives to reduce cardiovascular morbidity and mortality.

Physiological Control and Regulation Of Blood Pressure

Arterial BP is generated hemodynamically by the interplay between blood flow and the resistance to blood flow. As per Poiseuille's law related to hydraulic equation, it is defined mathematically as the product of cardiac output (CO) and total peripheral vascular resistance (TPVR): BP = CO x TPVR. CO is the major determinant of systolic BP (SBP), whereas TPVR largely determines diastolic BP (DBP). In turn, CO is a function of stroke volume, heart rate, and venous capacitance. Both CO and TPVR are controlled by the autonomic nervous system (ANS). BP fluctuates substantially with behaviour, but 24-h average BP is tightly regulated. Physiologically, in both normal and

hypertensive individuals, BP is maintained by moment-to-moment regulation of CO and TPVR exerted at three anatomic sites: arterioles, postcapillar venules (capacitance vessels), and heart. A fourth anatomic control site, the kidney, also contributes to mainte-nance of BP by regulating the volume of intravascular fluid. The CO is dependent on three regulated variables: end-diastolic volume, myocardial contractility, and heart rate. End-diastolic volume is the volume reached by the ventricular chamber before contraction and is determined by venous pressure, which is related to blood volume and venous smooth muscle tone, both of which are under sympathetic control (4). Myocardial contractility and heart rate are regulated by both the sympathetic and parasympathetic divisions of the ANS. In contrast, because blood vessels are not innervated by parasympathetic fibres, the para-sympathetic nervous system has little influence on vascular tone.

The neural control of BP operates via parasympathetic neurons that innervate the heart and via three main classes of sympathetic cardiovascular efferents – barosensitive, thermosen-sitive and glucosensitive that inner-vate blood vessels, the heart, the kidneys and the adrenal medulla. The barosensitive sympathetic efferents are under the control of arterial baroreceptors. This large group of efferents plays a dominant role in both short-term and long-term BP regulation. Their level of activity at rest is presumed to be the most crucial parameter for long-term BP control. This background activity is set by a core network of neurons that reside in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus and the nucleus of the tractus solitarius (NTS) (5, 6). Limbic, cortical and midbrain structures are responsible for rapid changes in sympathetic tone that relate to behaviour. It is generally assumed that these changes are not pertinent to the long-term regulation of BP, except in the context of stress-related hyper-tension. The BP is maintained within fairly narrows limits by a series of physiological reflexes that respond to both acute and chronic changes in BP. The two most important regulatory systems which control BP are:

1. The sympathetic nervous system
2. The renin-angiotensin-aldoste-rone system

Role of Sympathetic Nervous System in Regulation of BP

Cardiovascular sympathetic efferents can be broadly classified into three groups according to their dominant characteristics, the thermosensitivity; glucosensitivity; or barosensitivity (7-9). The thermosensitive group of cardiovascular efferents consists primarily of cutaneous vasdoconstrictors that are activated by hypothermia, emotional stimuli and hyperventilation (8, 10). The glucosensitive group controls adrenaline release from the adrenal medulla and is activated by hypoglycemia and physical exercise (11). These two types of cardiovascular efferent are only weakly, if at all, regulated by arterial baroreceptors, and presumably have a secondary role in short- and long-term BP stability. The third class, the barosensitive group of cardiovascular sympathetic efferents, irrespective of organ or tissue that they innervate, show ongoing activity at rest (sympathetic tone). They discharge bursts that are highly synchronized with the arterial pulse and respiration (10, 12, 13). Barosensitive sympathetic efferents control the heart and the kidneys, the release of noradrenaline from a subset of adrenal chromaffin cells, and constrict resistance arterioles, with the exception of those in the skin (8). Barosensitive efferents are responsible for short-term BP fluctuations (8, 14). They are also likely to be a key determinant of the long-term neural control of BP, in part because renin secretion, renal tubular sodium reabsorption and renal blood flow are apparently all under the control of this type of sympathetic efferent (12).

Barosensitive efferents are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to upright posture. Central sympathetic neurons arising from the vasomotor area of the medulla are tonically active. Carotid baroreceptors are stimulated by the stretch of the vessel walls brought about by the internal pressure (arterial BP). A sudden change in systemic BP is detected by baroreceptors in the aorta and carotid arteries. Afferent impulses from baroreceptors are integrated in the vasomotor centres of the sympathetic nervous system (Fig. 1). A rise in BP increases the input of impulses from the baroreceptors to the

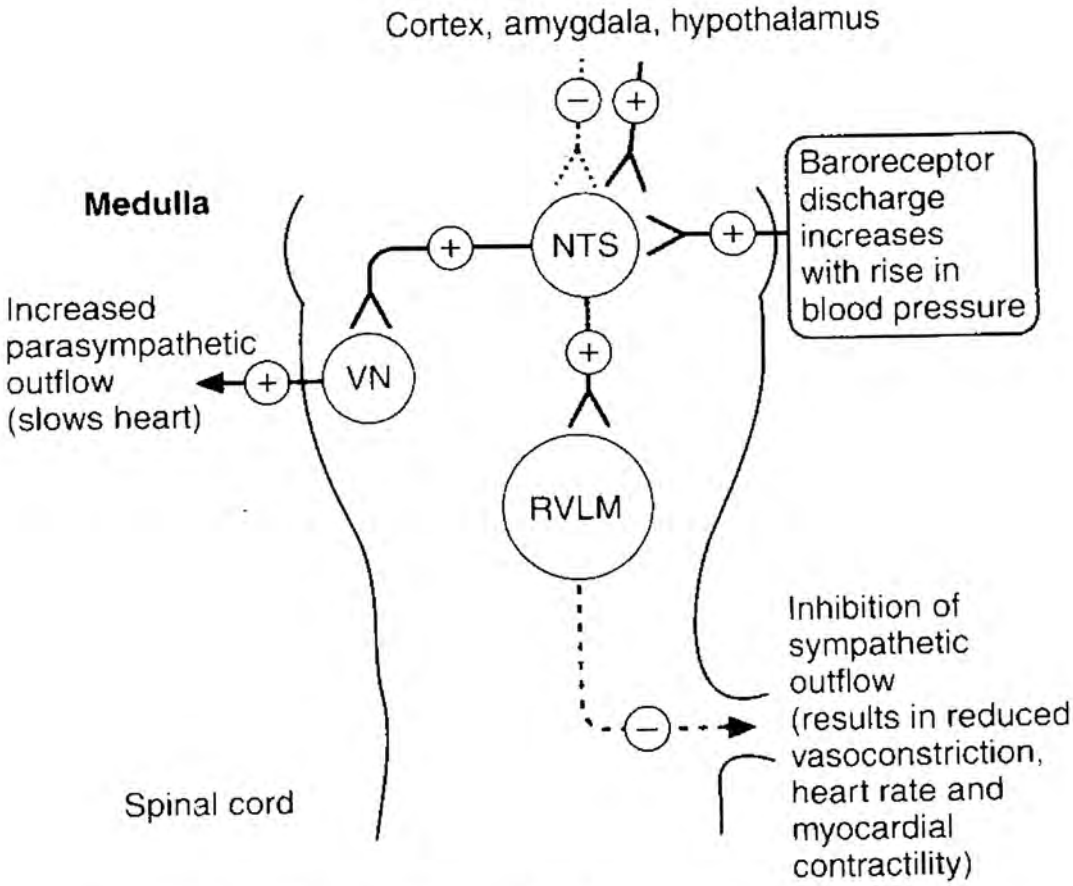


Figure 1. Physiological Control and Regulation of Blood Pressure
NTS, nucleus of the tractus solitarius; VN, vagal nucleus (cardioinhibitory centre); RVLM, rostral ventrolateral medulla, +, stimulation; –, inhibition.

vasomotor centres, resulting in decreased output from the centre and compensatory decrease in the efferent response of sympathetic nervous stimulation. Conversely, a reduction in stretch due to fall in BP results in a reduction in baroreceptors activity. Thus, in the case of a transition to upright posture, baroreceptors sense the reduction in arterial pressure that results from pooling of the blood in the veins below the level of the heart as reduced wall stretch, and sympathetic discharge is disinhibited. The reflex increase in sympathetic outflow acts through nerve endings to

increase peripheral vascular resistance (constriction of arterioles) and cardiac output (direct stimulation of the heart and constriction of capacitance vessels, which increases venous return to the heart), thereby restoring normal BP. The same baroreflex acts in response to any event that lowers arterial pressure, including a primary reduction in peripheral vascular resistance (e.g., caused by vasodilating agent) or a reduction in intravascular volume (e.g., due to hemorrhage or to loss of salt and water via the kidney).

Sympathetic efferents to the heart act mainly through beta-1 adrenoceptors to increase myocardial contractility and heart rate, generating a greater cardiac output. Efferents to arterial resistance vessels stimulate postsynaptic alpha-1 adrenoceptors, producing arteriolar vasoconstriction. This raises blood pressure and redistributes blood flow to specific vascular beds to maintain perfusion of vital organs (15). This redistribution is helped by beta-2 adrenoceptor-mediated vasodilation in selected vascular beds, such as skeletal muscle. Arterial vasoconstriction produces an increase in afterload on the heart but cardiac output is maintained by an increase in cardiac contractility. Stimulation of postsynaptic venous alpha-1 adrenoceptors constricts venous capacitance vessels. This increases venous return to the heart preload) improves cardiac output. If ventricular function is impaired cardiac output may fall (15).

2. Role of Renin-angiotensin-Aldosterone System in Regulation of BP

The sympathetic baroreflex mechanism is a feedback loop, the afferent limb of which involves mechanoreceptors that are activated by distention of the arterial wall (14). An increase in BP activates baroreceptors, thereby causing inhibition of cardiac, renal and vasomotor sympathetic efferents, which, in turn, leads to restoration of BP. The best known function of this reflex, together with its cardiovagal counterpart, is to dampen short-term BP fluctuations (14, 16, 17). However this reflex is also actively reset to allow BP to rise appropriately during certain behaviours such that the operating range is increased to higher BP levels without reduction in reflex sensitivity. Baroreflex resetting involves both neural and humoral mechanisms.

Role of Renin-Angiotensin-Aldesterone System (RAAS) in the Regulation of BP

A slower compensatory mechanism to overcome reduction in blood pressure is initiated by the release of renin from the juxtaglomerular apparatus of the kidney (Fig. 2). The major stimuli leading to renin release are reduced renal blood flow (often as a result of a decrease in blood pressure), decreased luminal Na^+ delivery or excess Na^+ in the distal renal tubule and direct sympathetic stimulation via beta-1 adrenoceptors at the juxtaglomerular apparatus.

Renin is a protease that acts on circulating renin substrate, the circularing 14-amino acid hepatic prohormone angiotensinogen to release the decapeptide angiotensin I. This in turn is cleaved by the carboxypeptidase, angiotensin-converting enzyme (ACE) located on the endothelial cell surface to release the octapeptide, angiotensin II. Angiotensin II has at least four physiological actions: (i) Stimulation of

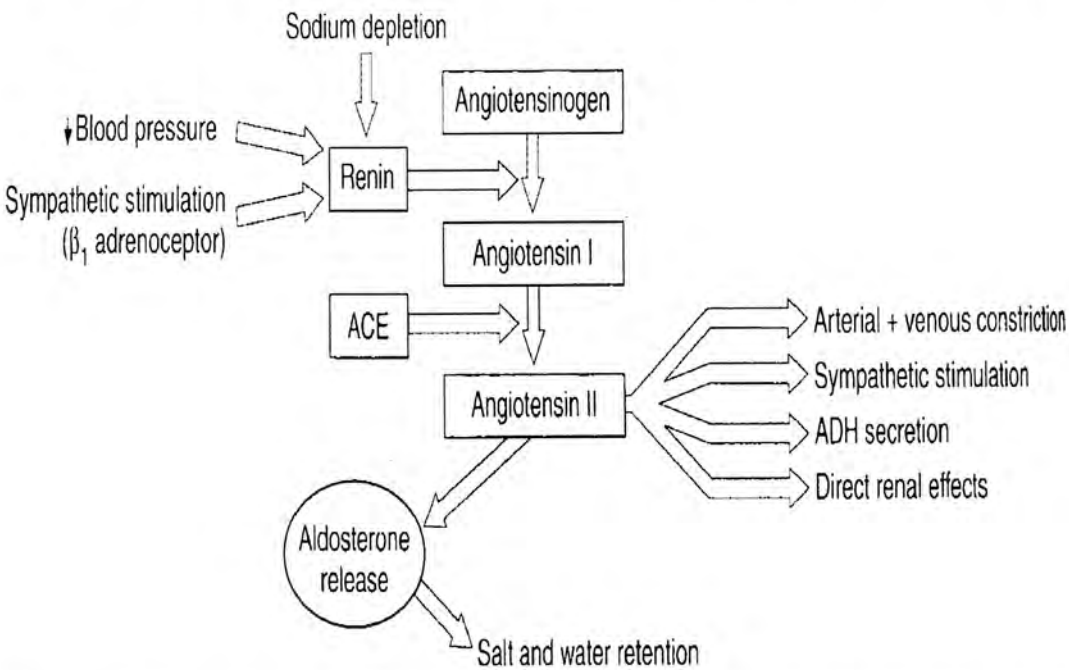


Figure 2. Role of rennin-angiotensin-aldosterone system in regulation of BP
ADH, antidiuretic hormone; ACE, angiotensin-converting enzyme.

aldosterone secretion by zona glomerulosa cells of the adrenal glands; (ii) increased reabsorption of NaCl at the proximal tubule and other nephron segments; (iii) Stimulation of thirst and ADH secretion; and (iv) arteriolar vasoconstriction, as a result of direct potent vasoconstriction and enhanced sympathetic nervous tone by an effect on presynaptic neurons. All of these effects are mediated by its action on type 1 Angiotensin II receptors (AT_1 receptors). By promoting the release of aldosterone, it acts on distal renal tubule to conserve salt and water at the expense of K^+ loss. Thus angiotensin II and aldosterone raise blood pressure by vasoconstriction and by increasing circulating blood volume (18, 19).

The integration of the sympathetic nervous system and renin-angiotensin-aldosterone responses to a fall in blood pressure is shown in Fig. 3. These mechanisms prevent hypotension due to peripheral pooling of blood on standing and during exercise.

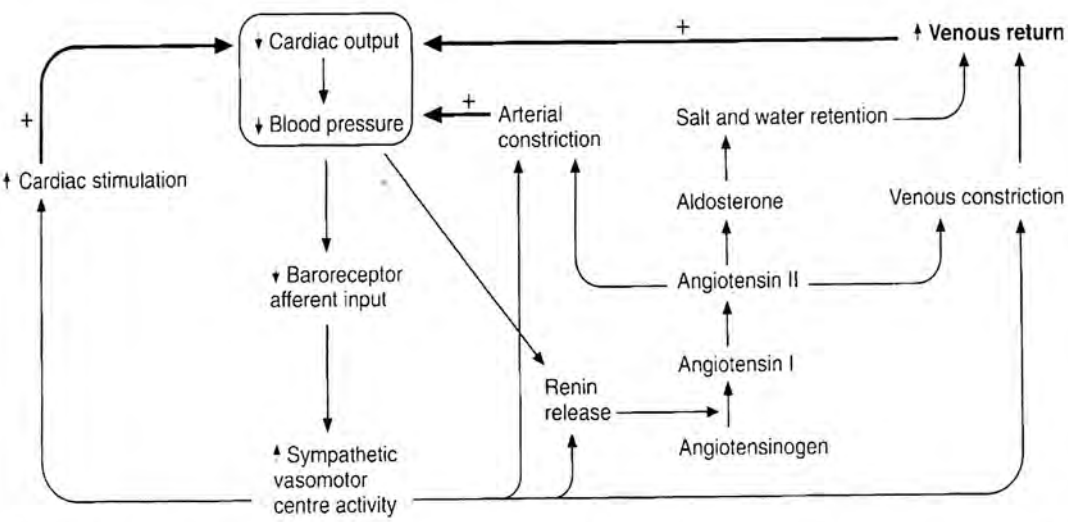


Figure 3. The control of blood pressure via the integration of sympathetic and renion-angiotensin-aldosteron system (RAAS). The sympathetic mediated responses on the left of the Fig. are rapidly responding events, whereas the RAAS events are more slowly responding. The final outcome are increased venous return, increased arterial constriction and increased cardiac output.

Additional Control Mechanism Involved In the Regulation of Vascular Volume And BP

A number of recent studies have shown that besides ANS and RAAS, there are some other control mechanism involved in the regulation of vascular tone and circulating blood volume, which include circulating or local hormones and metabolites such as atrial natriuretic peptide, prostaglandins, kinins, nitric oxide, endothelin, adenosine, etc. Their relative importance may differ in health and disease states. In addition, the vascular tone is also maintained by actin-myosin contractile apparatus of vascular smooth muscle cells which can be influenced not only by the circulating and local hormones as mentioned above but also by voltage-gated Ca^{2+} channels in the sarcolemma (20, 21).

Vascular Smooth Muscle Voltage-gated Calcium Channels

Like any other muscle, various regulators of vascular tone act by influencing actin-myosin contractile apparatus of vascular smooth muscle cells. This actin-myosin interaction leads to contraction and is regulated by the intracellular calcium (Ca^{2+}) concentration. A steep transmembrane gradient of Ca^{2+} concentration is maintained by the relative impermeability of the plasma membrane to Ca^{2+} ions and by membrane pumps that actively remove Ca^{2+} from the cytoplasm. Stimulation of vascular smooth muscle cells can increase the cytoplasmic Ca^{2+} concentration by two mechanisms. Firstly, Ca^{2+} can enter the cells by way of voltage-gated L-type calcium channels (VGCC) in the sarcolemma (22). Secondly, an increase in cytopalasmic Ca^{2+} can be released by intracellular Ca^{2+} from the sarcoplasmic reticulum. Constriction in the vascular smooth muscles is commonly initiated by the opening of VGCC in the sarcolemma during plasma membrane depolarization. The open Ca^{2+} channels mediate Ca^{2+} fluxes into the cytoplasm and activation of cytoplasmic protein, calmodulin (CaM) leading to the formation of Ca^{2+}-CaM complex which binds and activates myosin light chain kinase, which phospholyrates myosin-II light chains. When the light chain is phosphorylated the myosin head can slide over the active filament leading to smooth muscular contraction.

In contrast, relaxation of vascular smooth muscles occurs upon dephos-

phorylation of the myosin like chain. The process of dephosphorylation is potentiated with glutylyl cyclase is activated inside the smooth muscle cells. Activated guanylyl cyclase increases the production of cyclic guanosine 3',5'-monophosphate (cGMP). In turn the cGMP stimulates cGMP-dependent protein kinase, which then activates myosin light chain phosphatase. Dephosphorylation of the myosin light chain inhibits the sliding interaction of myosin head with actin, leading to smooth muscle relaxation (23).

Substances Elaborated in the Vascular Endothelium

Research in the past two decades has revealed several signaling molecules in the vascular endothelium to control vascular tone. Endothelial cells elaborate many signaling mediators and alter the expression of many genes in response to diverse stimuli (Fig. 4). Two of the most pharmacologically important signaling molecules which have been well defined in the recent past are nitric oxide and endothelin (24, 25).

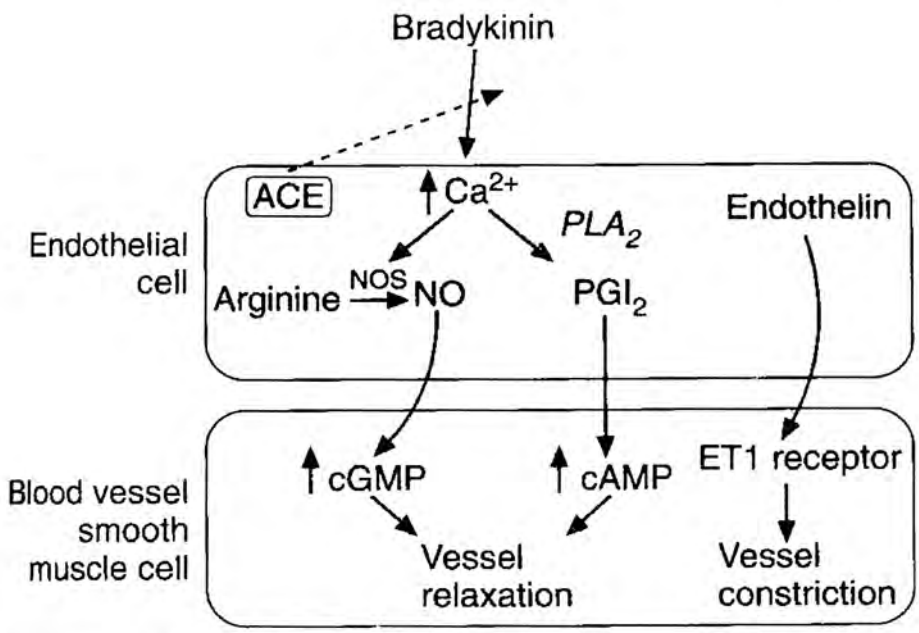


Figure 4. The endothelialy derived vasoactive substances involved in regulation of BP

Nitric oxide

The permissive role of endothelial cells in regulating vascular tone was first recognized with the observation that acetylcholine causes vasoconstriction when applied directly to de-endothelialized blood vessels, but causes vasodilatation when applied to normally endothelialized vessels (24). It was postulated that muscarinic cholinergic stimulation of the endothelium produces a relaxant molecule in the endothelial cell which diffuses to subjacent vascular smooth muscle cells to activate gunylyl cyclase. This vasodilatory compound was termed endothelial-derived relaxing factor (EDRF). Later EDRF was identified as nitric oxide (NO). Although acetylcholine was the first ligand to be identified that promotes NO synthesis in endothelial-cells, later on a number of other mediators which could do so were described. Shear stress, histamine, bradykinin, serotonin, substance P, ATP and sphingosine 1-phosphate can all produce increased NO synthesis by vascular endothelial cells. NO is synthesized by a family of Ca^{2+}-CaM-activated NO synthases (NOS). Endothelial NOS (eNOS) is responsible for endothelial-cell NO synthesis. This enzyme plays a critical role in controlling vascular tone and platelet aggregation. The importance of No in regulating vascular tone is underscored by the observation that eNOS-deficient mice are hypertensive.

Recent evidence suggest that NO may effect vasodilatation not only by activating guanylyl cyclase, but also by activating Ca^{2+}-dependent K^+ channels in vascular smooth muscle cells. NO appears to activate these K^+ channels directly via a guanylyl cyclase-independent mechanism leading to hyperpolarization of the cells and subsequently, to vasodilatation.

Endothelin

Endothelin, a 21-amino acid vasoconstrictor peptide is a potent endothelium-derived vasoconstrictor (25). This peptide is considered a functional 'mirror-image' of NO as the latter is a potent endothelium-derived vasodilator. Besides its effect on vasculature, endothelin has positive inotropic and chronotropic actions on the heart and also contributes to remodeling within the cardiovascular system. Proposed mechanisms of endothelin-induced remodeling include neointimal proliferation and increased collagen deposition leading to fibrosis. Three isoforms of endothelin ET-1, ET-2 and ET-3 have been identified. The ET-1 produced by endothelial cells

(and vascular smooth muscle cells under inflammatory conditions) is mainly involved in cardiovascular actions – acting locally in a paracrine or autocrine fashion. Local ET-1 concentration within the vascular wall is more than 100 times greater than that in the circulation, because it is secreted mainly on the basal side of endothelial cells. Endothelins are known to act through to endothelin receptor subtypes, ET_A and ET_B. Both receptors are G protein-coupled receptors, whose effectors likely involve phospholipase C-mediated pathways. ET_A receptors on vascular smooth muscle cells mediate vasoconstriction, whereas ET_B receptors are located predominantly on vascular endothelial cells, where they mediate vasodilatation via the release of prostacyclin and NO. ET_B receptors are also found on vascular smooth muscle cells, where they mediate vasoconstriction. Thus, endothelins produce vasoconstriction by acting through both ET_A and ET_B receptors in the vascular smooth muscles and vasodilatation by acting through ET_B receptor in the endothelium.

Neurohormonal Mechanisms

Besides the angiotensin II as described above, circulating catecholamines from the adrenal gland (adrenaline and noradrinaline) can influence vascular tone via alpha-1 and beta-2 adrenergic receptors on vascular smooth muscle cells. In addition vasopressin or antidiuretic hormone (ADH) secreted in response to angiotensin II affects the vascular tone by acting on its 3V types of receptors. V_{1a} receptors mediate the vasoconstrictor action of ADH; V_{1b} potentiate the release of ACTH by pituitary corticotropic cells; and V_2 receptors mediate the further release of ADH to increase intravascular volume. All these actions of ADH play a minor role regulating the BP in certain situations (26).

Homeostatic Autoregulatory Mechanisms

A number of locally controlled mechanisms also modulate vascular tone. These homeostatic autoregulatory mechanisms in vascular smooth muscle respond to increases or decreases in perfusion pressure by vasoconstriction or vasodilation, respectively to preserve blood flow at a constant level. (Blood Flow = Perfusion Pressure/Resistance). Vascular tone, and thus blood flow, is governed by metabolites – such as H^+, CO_2, O_2, adenosine, lactate and K^+ – produced in surrounding tissue. Local mechanisms of vascular tone regula-

tion predominate in the vascular beds of essential organs (e.g. heart, brain, lung, and kidney), so that blood flow, and thus O_2 supply, can be adjusted quickly to meet the demand of local metabolism in these organs (27).

Role of Natriuretic Peptides in Regulating Blood Pressure

Tho atria and other tissues of mammals contain a family of peptides with natriuretic, diuretic, vasorelaxant and other properties (28). This family of peptides consist of atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptide (CNP). ANP, a 28-amino acid peptide is synthesized primarily in cardiac atrial cells, but small amounts are also synthesized in ventricular cells. It is also synthesized by neurons in the central and peripheral nervous systems and in the lungs. Several factors which increase the release of ANP from the heart are - atrial stretch via mechanosensitive ion channels, blood volume expansion, head-out water emersion, changing from standing to supine position and exercise (28). ANP release can also be increased by sympathetic stimulation via alpha-1a adrenergic receptors, endothelins via ET_A receptor subtype, glucorticoids, and vasopressin. A rise in plasma ANP is also seen in various pathological states, like heart failure, primary aldosteronism, chronic renal failure and inappropriate ADH secretion syndrome. As described above ANP produces marked increases in sodium excretion and urine flow. The ANP-induced natriuresis is apparently due to both the increase in the glomerular filtration and decrease in proximal tubular sodium reabsorption. Several effects of ANP also decreases arterial BP. Besides its action on kidney, a number of other effects which contribute to its hypotensive actions are: (i) inhibition of the secretion of renin, aldosterone and vasopressin (which all increase sodium and water excretion), (ii) decrease in sympathetic tone to the peripheral vasculature and antagonism of vasoconstrictor action of angiotensin II and other vasoconstrictors, and (iii) a direct vasodilatory action resulting from stimulation of guanylyl cyclase activity leading to increased cGMP and decrease cytosolic Ca^{2+}concentration. There is considerable evidence that ANP participates in the physiological regulation of sodium excretion and blood pressure, e.g. suppression of ANP production or blockade of its action impairs the natriuretic response to volume expansion, and increases blood pressure (28).

Patho-Physiological Mechanisms in the Development of Hypertension

Hypertension is a heterogeneous medical condition. In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension). Some of the suggested mechanisms for the development of essential hypertension have been elaborated in Table 1. While this form of hypertension cannot be cured, it can be controlled.

Table 1. Patho-physiological Mechanisms in the Development of Hypertension

Blood pressure is the mathematical product of cardiac output and peripheral resistance. Increased BP can result form increased cardiac output and/or increased total peripheral resistance.	
Increased cardiac output	Increased cardiac preload: • Increased fluid volume for excess sodium intake or renal sodium retention (from reduced number of nephrons or decreased glomerular filtration) Venous constriction: • Excess stimulation of the RAAS • Sympathetic nervous system over activity
Increased peripheral resistance	Functional vascular constriction: • Excess stimulation of the RAAS • Sympathetic nervous system over activity • Genetic alterations of cell membranes • Endothelial-derived factors Structural vascular hypertrophy: • Excess stimulation of the RAAS • Sympathetic nervous system over activity • Genetic alterations of cell membranes Endothelial-derived factors Hyperinsulinemia resulting from obesity or the metabolic syndrome

Essential Hypertension

Over 90% of individuals with hypertension have essential hypertension (primary hypertension) (29). Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. Hypertension often runs in families, indicating that genetic factors may play an important role in the development of essential hypertension (30). Data suggest that there are monogenic and polygenic forms of BP dysregulation that may be responsible for essential hypertension. (31, 32). Many of these genetic traits feature genes that affect sodium balance (32), but genetic mutations altering urinary kallikrein excretion, nitric oxide release, aldosterone excretion, other adrenal steroids, and angiotensinogen are also documented (31). In the future, identifying individuals with these genetic traits could lead to alternative approaches to preventing or treating hypertension.

Insulin resistance and hyperinsulinaemia as a cause of primary hypertension

In some patients evidence has linked insulin resistance and hyperinsulinaemia with the development of essential hypertension, sometimes referred to as the metabolic syndrome (33). Hypothetically, increased insulin concentrations may lead to hypertension because of increased renal sodium retention and enhanced sympathetic nervous system activity. Moreover, insulin has growth hormone-like actions that can induce hypertrophy of vascular smooth muscle cells. Insulin also may elevate BP by increasing intracellular calcium, which leads to increased vascular resistance. The exact mechanism by which insulin resistance and hyperinsulineamia occur in hypertension is unknown. It has been suggested that insulin resistance may be the consequence of chronic sympathetic activation. Sympathetic activation generates vasoconstriction an, secondarily, a thickening of arterioles, which lead to less smooth muscle perfusion. Consequently, muscle use of glucose is reduced because fast-contracting fibres become less sensitive to insulin due to beta-adrenergic hyperactivity. The pancreas responds by acute secretion of insulin. Sympathetic activation observed in the obese patient could, in certain cases result from a cerebral action of leptin, secreted in excess by adipocytes (34).

Secondary Hypertension

Fewer than 10% of patients have a specific cause of their hypertension, termed as secondary hypertension where either a comorbid disease or a drug is responsible for elevating BP (Table 2). In most cases renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause (35). Table 2 describes some of the prescription drugs and potential secondary causes that are either

Table 2. Secondary Causes of Hypertension

Disease	Drugs and food substances associated with hypertension in humans
Chronic kidney disease Cushing's syndrome Coarctation of the aorta Obstructive sleep apnea Parathyroid disease Pheochromocytoma Primary aldosteronism Renovascular disease Thyroid disease	**Prescription drugs** Corticosteroids; Estrogens (oral contraceptives with high estrogenic activity); NSAIDs, COX-2 inhibitors; Phenylpropanolamine and analogues; Cyclosporine and tacrolimus; Erythropoetin; Sibutramine; Antidepressants (especially fluoxetine, venlafaxine); bromocriptine; buspirone; carbamazepine; clozapine; desfulrane; ketamine, metoclopramide; Clonidine/beta-blocker combination, Pheochromocytoma: beta-blocker with alpha-blocker first **Street drugs and other natural products** Cocaine and cocaine withdrawal; Ma huang (herbal ecstasy); Nicotine and withdrawal; Anabolic steroids, Narcotic withdrawal, Methylphenidate, Phencyclidine, Ketamine, Ergotamine and other ergot-containing herbal products, St. John's wort. **Food substances** Sodium, Ethanol, Tyramine-containing foods if taken with a monoamine oxidase inhibitor, Licorice **Chemical elements and other industrial chemcials** Cadmium, Lead, Lithium, Mercury, Thallium

concurrent medical conditions or are endogenously induced diseases. If the cause of the secondary hypertension can be identified, hypertension in these patients potentially can be cured.

Antihypertensive Drugs

Principal classes of antihypertensive drugs and their sites of action is given in Table 3 and Figure 4.

Table 3. Principal classes of antihypertensive drugs and their sites of action

Site of action	Drug class	Drugs
Sympathetic nervous system	β-Adrenoceptor antagonists (β-blockers)	Atenolol, Propranolol, Pindolol
	α_1-adrenoceptor antagonists (α_1-blockers)	Prazosin, Doxazosin
	Selective imidazoline receptor agonists	Moxonidine
	Centrally acting α_2-adrenoceptor agonists	Methyldopa, Clonidine
Blockers of Rennin-Angiotensin-Aldosterone System (RAAS)	Antiotensin-converting enzyme (ACE) inhibitors	Captopril, Enalapril, Rampril, Lisinopril, Perindopril
	Angiotensin II receptor antagonists	Losartan, Candesartan
Vasodilatation by other mechanisms	Diuretics	Hydrochlorothiazides, Chlorthalidone, Bendrofluazide, Indepamide, Furosemide, Bumetinide
	Calcium channel antagonists	Amlodepine, Nifedipine, Diltiazem, Verapamil
	Potassium channel activators	Minoxidil, Cromakalim, Penacidil, Nicorandil
	Nitrovasodilators	Nitroprusside
	Endothelin antagonists	Bosantan, Sitaxentan, Ambrisentan, Tezosentan, Phosphoramidon (ECE-I)

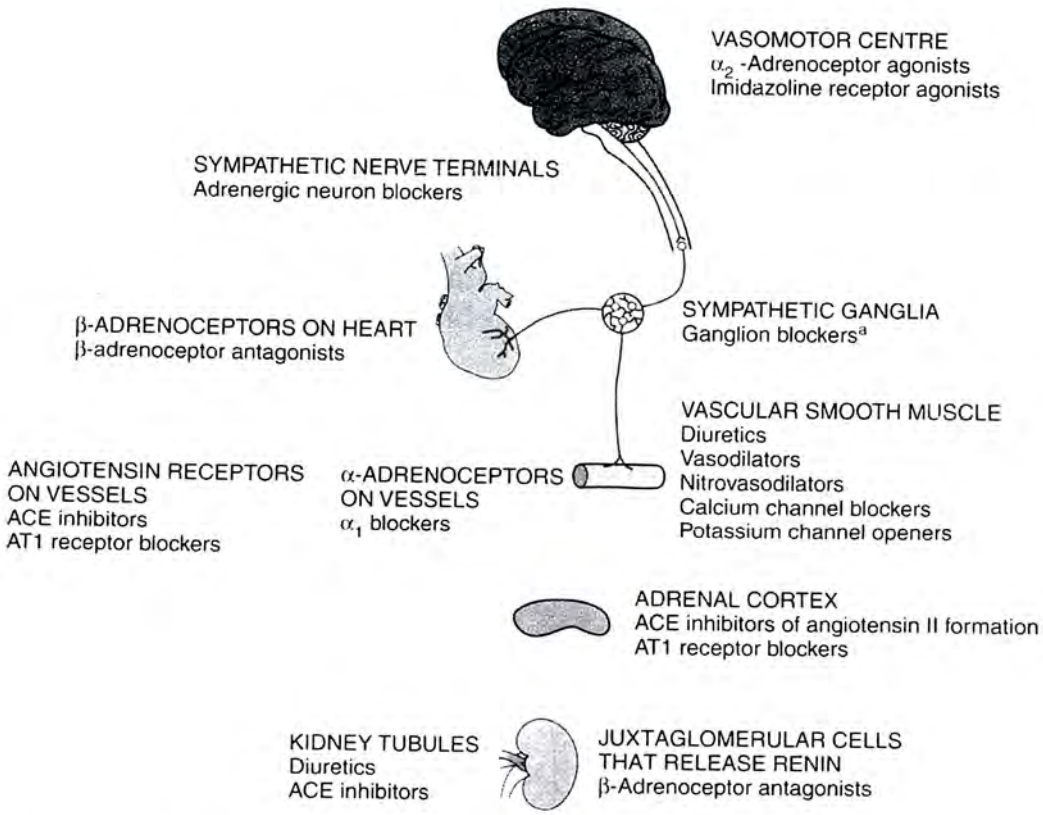


Figure 5. Principal classes of antihypertensive drugs and their sites of action

Drugs Acting on Sympathetic nervous system

β-Adrenoceptor antagonists (β-blockers)

Mechanism of action

- Reduction of heart rate and myocardial contractility, which decrease cardiac output
- Blockade of renal juxtaglomerular beta-1-adrenoceptors, which reduces renin secretion
- Peripheral vasodilatation, produced by compounds with beta-2-adrenoceptor partial agonist activity, e.g. pindolol
- Blockade of presynaptic beta-adrenoceptors in sympathetic nerves supplying arteriolar resistance vessels may reduce the outflow of noradrenaline but the importance of this is clinically uncertain.

- Decrease in central sympathetic flow to periphery by blocking beta-receptors in brain

Alpha-1-adrenoceptor antagonists (α_1-blockers)

Mechanism of action: Blockade of postsynaptic alpha-1-adrenoceptors lowers blood pressure by:

- Reduced tone in arteriolar resistance vessels
- Dilating venous capacitance vessels, which reduces venous return and, therefore, cardiac output
- The fall in BP is detected by arterial baroreceptors, which initiate reflex sympathetic stimulation.
- Selective alpha-1-adrenoceptor antagonists do not block the inhibitory presynaptic alpha-2-adrenoceptors on sympathetic nerve terminals.

Selective imidazoline receptor agonists

Mechanism of action

- Imidazoline I-2 receptors are concentrated in the RVLM, a part of the brain stem for centre are important for sympathetic drive
- Increased neuronal activity in this area, either through baroreceptors stimulation or by direct stimulation of I-1 receptors, will decrease sympathetic outflow and increase vagal tone.
- This results in reduction in BP with no reflex tachycardia

Centrally acting α_2-adrenoceptor agonists

Mechanism of Action:

- The alpha-2-agonists reduce central sympathetic nervous outflow from the medullary vasomotor centre which reduces both arterial and venous tone (TPVR).
- Methyldopa by its conversion to methylnoradrenaline and clonidine directly stimulate central presynpatic alpha-2-adrenoceptor which inhibit neurotransmitter release by negative feedback.
- Clonidine also acts on imidazoline I-1 receptors. In high doses it also has peripheral postsynaptic alpha-1-adrenoceptor agonist activity, which produces direct peripheral vasoconstriction; this initially may offset some of the BP lowering effect.

Blockers of Renin-Angiotensin-Aldosterone System (RAAS)

Antiotensin-converting enzyme (ACE) inhibitors

Mechanism of Action: The ACE inhibitors act by several mechanisms

- Competitive inhibition of ACE reduces generation of angiotensin II and consequently reduces the release of adosterone. Inhibition of tissue ACE in vascular wall (rather than plasma ACE) is most important for the hypotensive effect of these drugs. Reduced tissue concentrations of he angiotensin II leads to arterial and, to a lesser extent, venous dilatation.
- Lack of reflex tachycardia may be because of stimulation of the vagus nerve or because of reduced potentiation of sympathetic nervous activity by angiotensin II
- Angiotensin II is also implicated in the development of arterial and left ventricular hypertrophy in hypertension. The importance of ACE inhibitors compared with other antihypertensives in limiting these effects is uncertain
- ACE also degrades vasodilator kinins. Increased kinins or vasodilator prostaglandins and NO in the vascular wall may contribute to the hypotensive action of ACE inhibitors.

Angiotensin II type I receptor antagonists

Mechanism of action

- The angiotensin receptor antagonists are selective for the AT_1, receptor subtype, which is found in the heart, blood vessels, kidney, adrenal cortex, lung and brain.
- They have less effect at a second receptor subtype, known as AT_2, which is believed to be involved in regulation of vascular growth in response to angiotensin II.
- Reduced generation of the intracellular second messengers diacylglycerol and inositol triphosphate in target cells is responsible or the actions of these drugs.
- The effects show similarities to those produced by ACE inhibitors, except that kinin degradation is unaffected by angiotensin II antagonists, and inhibition of the effects of angiotensin II on the AT_1 receptor is more complete.

Vasodilatation by other mechanisms

Diuretics

Mechanism of Action

There are several actions involved in lowering blood pressure:

- An initial hypotensive effect is produced by intravascular salt and water depletion. However, compensatory mechanisms such ass activation of the renin-angiotensin-aldosterone system largely restore plasma and extracellular fluid volumes (unless salt and water retention was a major component of the initial hypertension e.g. in advanced renal failure or as a consequence of other antihypertensive treatment).
- Direct arterial dilatation is responsib le for the longer-term reduction in blood pressure. Vasodilatation may result from reduced CA^{2+} entry into the smooth muscle of the arteriolar resistance vessel walls (perhaps as a consequence of Na^{+} depletion) and from synthesis of the vasodilator prostaglandins PGE_2 and PGI_2.

Calcium channel antagonists

Mechanism of Action

- The voltage-gated Ca^{2+} L-channel antagonists lower blood pressure principally by arterial vasodilatation by preventing the Ca^{2+} fluxes into the vascular smooth muscle cells.

Potassium channel activators

Mechanism of Action

- Minoxidil activates cell membrane potassium channels leading to potassium accumulation in the cell and hyperpolarisation of cell membrane.
- Minoxidil is one of the most powerful peripheral arterial dilators

Nitrovasodilators

Mechanism of Action

- Nitroprusside is a nitrovasodilator with a mechanism of action similar to that of organic nitrates
- It produces dilatation of aerterioles and veins, reducing both peripheral resistance and venous return
- Its use is limited to the emergency management of some hypertensive states

Endothelin antagonists

Mechanism of Action

- By blocking the ET_A (vasoconstrictors) and ET_B

(vasodilators), these agents produce a fall in BP and are in the process of development and available for research use.

- These agents are Bosantan, Sitaxentan, Ambrisentan and Tezosentan which act by blocking ET receptors, whereas Phosphoramidon is a **E**ndothelin **C**onerting **E**nzyme-**I**nhibitor (ECE-I), an agent which block the processing of ET from its pre-pro-peptide structures.

Preventive Interventions for Hypertension

Physical inactivity (sedentary state) per se has been suggested to a risk factor for cardiovascular diseases. Subjects with low levels of physical fitness had a relative risk of 1.52 for development of hypertension when compared with subjects with high levels of fitness. A vast epidemiological literature describes an apparent relationship between raised BP and lifestyle choices and habits. Several nonpharmacological interventions are recommended for primary prevention of hypertension and other cardiovascular diseases. Regular moderate physical aerobic exercises, such as walking, jogging, cycling or swimming and dietary modifications such as reduced intake of sodium chloride (salt), reduced alcohol consumption, and possible increased dietary potassium, calcium, magnesium and fish oil, are some of the suggested life style interventions which have been shown to reduce the BP in patient with mild essential hypertension in a number of randomized controlled trials.

Physical aerobic exercise

Regular aerobic exercise of moderate intensity decreases systolic BP by 6-10 mmHg and diastolic BP by 4-8 mmHg in patients with essential hypertension and have been demonstrated to prevent the cardiovascular mortality and morbidity. The WHO/ international Society of Hypertension and seventh report of the JNC of High BP recommend exercise at an intensity of ~50% of maximum oxygen consumption (Vo_{2max}) for 30 min per time, and 5-7 times per week, for patients with mild to moderate essential hypertension. According to these guidelines, the beneficial effects of exercise appear after 10 weeks when patients perform exercise for at least 30 min per time and at least 3 times per week.

Mechanism of action of Physical aerobic exercise in improving the BP and cardiovascular disease status: Some of the beneficial effect of exercise

is improvement in endothelial function through (36, 37 and ref. therein):

- An increase in NO bioavailability (increase in NO production and/ or decrease in NO inactivation) by a number of mechanisms,
- Increase in capillary density and the capillary-to-fibre ratio in skeletal muscle in humans,
- Decrease in reactive free oxygen (RFO)-radicals due to up-regulation of antioxidant system,
- Inactivation of NADH/NADPH oxidase system which may contribute to the improvement in endothelial function.
- Increased synthesis vasodilatory prostaglandins – PGI_2 and PGE_2 and endothelium-derived hyperpolarizing factor (EDHF)
- Reduction in weight, insulin resistance and insulin levels, and increase in HDL cholesterol

Mechanism of action of dietary modifications in improving the BP and cardiovascular disease status: Although a number of dietary modifications have been advised, it is difficult to ascertain which specific choices have clinically important influences on BP as such factors are often inter-related. Further patients may not follow regimens designed to change dietary habits. The available evidence suggests that patients should be encouraged to:

- Follow weight reducing diet which is low in fat and high in fruits and vegetables
- Restrict their dietary sodium intake to under 6 g/day, by avoiding processed foods with high salt content and by adding less salt to food or substituting low-sodium slat
- Overweight patients should be encouraged to lose weight through a low-calorie diet
- A reduction in BP (about 2 mm Hg) was observed to be associated with fish oil supplements and high calcium, magnesium, potassium diet. All these maneouvers have been shown to improve the endothelial function by reducing the vasoconstrictor response to a number of agents. Since fish oil supplements are not cost effective, it may be more appropriate to recommend a fatty fish in healthy diet (38 and ref. therein).

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Hypertension in Elderly

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Abstract

The elderly, one of the fastest-growing segments of the population, have the highest prevalence of hypertension and account for a large proportion of persons seeking antihypertensive treatment. Arterial stiffness is increased by aging and this process is accelerated by hypertension. The effects of aging are seen almost exclusively in the central elastic arteries, principally the aorta. Systolic and pulse pressures are the major predictors of cardiovascular outcome in the elderly. Current recommendations suggest that both systolic and diastolic hypertension should be treated in elderly. Although individualization is necessary for patients older than 80 years of age the target should be to achieve systolic pressure of less than 140mmHg and diastolic pressure of less than 90 mm Hg. The focus should be on achieving blood pressure control, not initial therapy. Low-dose thiazide or calcium channel drugs are good as initial therapy. Multiple medications are usually required in older patients, and combinations should be based on concomitant diseases Drug dosing regimens should be adjusted for age- and disease-related changes in drug metabolism and potential drug-drug interactions Patients should be monitored for adverse effects and drug interaction. With all drugs, orthostatic hypotension should be avoided because of the increased risk of falling in older patients. Other concerns include postprandial hypotension, hypovolemia with diuretics, and hyperkalemia with angiotensin-converting enzyme, angiotensin receptor blocker, or aldosterone antagonists.

Key Words : effects of aging, arterial stiffness, systolic and diastolic hypertension, drug interaction

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The elderly, one of the fastest-growing segments of the population, have the highest prevalence of hypertension and account for a large proportion of persons seeking antihypertensive treatment. Arterial stiffness is increased by aging and this process is accelerated by hypertension. The effects of aging are seen almost exclusively in the central elastic arteries, principally the aorta. Systolic and pulse pressures are the major predictors of cardiovascular outcome in the elderly. Current recommendations suggest that both systolic and diastolic hypertension should be treated in elderly. Although individualization is necessary for patients older than 80 years of age the target should be to achieve systolic pressure of less than 140mmHg and diastolic pressure of less than 90 mm Hg. The focus should be on achieving blood pressure control, not initial therapy. Low-dose thiazide or calcium channel drugs are good as initial therapy. Multiple medications are usually required in older patients, and combinations should be based on concomitant diseases Drug dosing regimens should be adjusted for age- and disease-related changes in drug metabolism and potential drug-drug interactions Patients should be monitored for adverse effects and drug interaction. With all drugs, orthostatic hypotension should be avoided because of the increased risk of falling in older patients. Other concerns include postprandial hypotension, hypovolemia with diuretics, and hyperkalemia with angiotensin-converting enzyme, angiotensin receptor blocker, or aldosterone antagonists.

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Introduction

Longevity has been one of the greatest achievements of the 20th century. There are more older people today than ever before and their number is on the increase The world's population age 65 and older is growing by an unprecedented 800,000 people a month, according to a report from the U.S. Census Bureau and the National Institute on Aging. The report, "An Aging World: 2001," predicted that this phenomenon of global aging will continue well into the 21st century, with the numbers and proportions of older people continuing to rise in both developed and developing worlds. There are 77 million old people in India. This number is likely to rise to 177 million by 2025. Adults aged 65 and older are disproportionately affected by hypertension, dyslipidemia, and diabetes, which are established risk factors for cardiovascular disease (CVD). Although risk reduction strategies among older adults, including control of CVD risk factors, can lead to a decline in premature CVD morbidity and mortality, the prevalence of these risk factors has generally increased in the past decade among elders and risk factor control rates have been suboptimal (1). The prevalence of hypertension in elderly subjects (age greater than 60 to 65 years) is as high as 60 to 80 percent. The lifetime risk of developing hypertension in individuals aged 55 to 65 who do not have hypertension is approximately 90 percent. Systolic pressure rises and the diastolic pressure fall after age 60 in both normotensive and untreated hypertensive subjects.

Aging and arterial stiffness

Aging has a greater effect on arterial stiffening than any other process. The effects of aging are seen almost exclusively in the central elastic arteries, principally the aorta, which also dilates progressively with age. In a normal cohort of subjects in Sydney and Beijing, aortic PWV increased twofold between ages 15 and 70 years. Studies in communities where salt intake and prevalence of hypertension are low, has shown a far less increase in aortic wave velocity with age. These findings suggest that high salt intake and hypertension accelerate the aging process. Studies of arterial distensibility have shown the same marked difference between central elastic and peripheral muscular arteries with age. Other manifestations of arterial stiffening associated with aging include increases in brachial pulse pressure (by 60 to 100%

in the Framingham cohort between 35 and 80 years-as compared with a 3 to 10% increase in mean pressure), together with increases in radial, carotid, and aortic systolic pressure augmentation.

Concomitant increases in diameter and stiffness (2) of elastic arteries with age suggest a common cause. Aging is associated with fracture and fragmentation of the elastin fibres or lamellae within the media (3). Other remodeling changes including increases in collagen and glycosaminoglycans-appear to be secondary. It has been suggested that the changes in stiffness and caliber are due to fatigue and fracture of the elastic lamellae, with progressive dilatation of the aorta and recruitment of collagenous fibers within the arterial wall (4). The inert elastic fibers, whose half-life is measured in decades, fracture after multiple cycles of stretch, like rubber and other elastic materials (5). Calculations based on the properties of rubber indicate that elastic fiber, subject to 10% stretch over 800×10^6 cycles (approximately 25 years at heart rate 70/ min), will fracture, whereas elastic fibers in a peripheral artery that stretch less than 5% with each cycle will not fracture over 3000×10^6 cycles, i.e., in 100 years. This theory, which is well established in the physical sciences, explains observations for the aorta and central elastic arteries and the differences between the central arteries and the differences between the central arteries, where distension in early life is approximately 10% with each heartbeat, and the peripheral muscular arteries, where the pulsatile change in diameter is less than 5%. The theory also explains how damage to the elastic lamellae may be accelerated in aortic coarctation and in some other hypertensive states in which pulsatile aortic strain is increased (3).

Hypertension, Aging and Arterial Stiffness

Arterial stiffness is increased by aging and this process is accelerated by hypertension. Changes in arterial stiffness with age are apparent as an increase in pulse wave velocity. Studies in normotensive and hypertensive subjects have shown a relation between left ventricular hypertrophy and arterial stiffness (6). Progressive arterial stiffening with age is considered responsible for the progressive left ventricular hypertrophy in aging human subjects. Stiffness and characteristic impedance of the aorta and large elastic arteries

increase with elevation in arterial pressure. In the early stage of hypertension, compliance of peripheral muscular arteries may be paradoxically increased as a result of passive arterial dilatation. Changes are largely due to the physical effect of increased arterial pressure per se (increased stiffness at higher pressure) and are largely reversed by antihypertensive therapy. They are the same changes seen with aging-early return of wave reflection, greater augmentation of the central aortic and cartoid pulse, and shift of ascending aortic impedance curves upward and to the right. Increase in aortic augmentation is associated with increase in height of the secondary systolic pressure wave in the radial artery, causing it to be as high as or higher than the initial pressure peak. This was recognized by Mahomed in his sphygmographic studies of hypertension in 1874 as the most consistent feature of hypertension: "The tidal wave is prolonged and too much sustained" (7).

Arterial stiffening in hypertension may be increased by the structural degeneration caused by prolonged high arterial pressure. Arterial degeneration, medial necrosis, and aneurysm formation are accelerated by hypertension. In conditions such as aortic coarctation and hyperdynamic states, this can be explained on the basis previously proposed for aging change-greater pulsatile strain over hundreds of millions of cycles. Inhomogeneties in the arterial wall-as at bifurcations where a muscular coat is deficient-may allow greater stretch of elastin fibres and predispose to early fracture of elastin fibers and aneurysm formation. A study at PGIMER, Chandigarh showed that pulse wave velocity increased significantly in hypertensive patients as compared to controls and an increase in age and deranged lipid profile were associated with significant increase in pulse wave velocity (8).

Special issues in Elderly people with Hypertension

1. Isolated systolic hypertension (ISH): It has been generally defined as an elevated systolic pressure above 160 mmHg, with a diastolic pressure that is below 90 mmHg. However, the majority of experts believe (Seventh Joint National Committee report) that the systolic level of 140 mm Hg is the upper limit of normal at all ages and ISH accounts for 60 percent of cases of hypertension in the elderly. Furthermore, the

systolic and pulse pressures may be the major predictors of outcome in the elderly.

2. Pseudohypertension: This is a condition in which there is a major discrepancy between intra-arterial and arm-cuff blood pressures, such that cuff pressures are falsely high should be suspected in older patients who, despite high blood pressure measurements, have minimal vascular damage in the retina and who experience inordinate postural dizziness despite cautious therapy.

3. Variability of blood pressure: Blood pressure readings are far more variable in the elderly, so more readings should be taken initially than for patients in the general population.

4. Postural Hypotension: Blood pressure should be measured in both the sitting and standing positions since there is a high frequency (as much as 30%) of a 20 mm Hg or greater fall in blood pressure in patients with a systolic pressure over 160 mm Hg. Postural hypotension of greater than 20 mm Hg or 20 percent of systolic pressure is a risk factor for falls and fractures that carries significant morbidity and mortality. Elderly patients may have sluggish baroreceptor and sympathetic nervous responsiveness, as well as impaired cerebral autoregulation.

   Antihypertensive medications, anti-parkinsonian agents, antipsychotic agents and tricyclic antidepre-ssant drugs add to development of postural hypotension. In these circumstances standing blood pressure should be used to guide treatment decisions. Postural blood pressure changes should be assessed (after >5 minutes supine, immediately after standing, and 2 minutes after standing) in older patients, and volume depletion avoided. Side effects like dizziness and lightheadedness should alert the investigator of possible overtreatment. Postprandial declines in both systolic and diastolic blood pressure occur about 1 hour after eating, with blood pressure returning to fasting levels 3 to 4 hours after eating.

5. Comorbid conditions Hypertension is a common comorbidity in persons with diabetes mellitus,

and its prevalence increases with advancing age. Both diabetes mellitus and hypertension are independent risk factors for development in older persons of coronary artery disease, ischemic stroke, peripheral arterial disease, and of congestive heart failure. Presence of other comorbid conditions related to nervous, respiratory, cardiac, genitourinary and gastrointestinal systems are common and may make the treatment difficult and complex.

6. Vascular cognitive impairment (VCI): It is the modern term related to vascular burden of the brain, reflecting all encompassing effects of cerebrovascular disease (CVD) on cognition. VCI (9) encompasses mild deficits in one or more cognitive domains to a broad dementia like syndrome. Vascular risk factors include arterial hypertension, high cholesterol, and diabetes. In the Rotterdam Scan Study (10), current hypertension or established hypertension of 5- to 20-year duration were associated with significantly increased white matter lesions.

7. Diastolic Heart Failure- There has been growing recognition over the past two decades that a substantial proportion of patients who have heart failure, particularly the elderly, have preserved systolic left ventricular function (11). This condition has been presumptively termed diastolic heart failure. Several lines of evidence suggest that systemic hypertension plays an important role in the genesis of this clinical syndrome. Acute pulmonary edema in these patients most likely is because of an exacerbation of diastolic dysfunction caused by severe systolic hypertension.

Management

Despite numerous outcome trials demonstrating the benefits of BP lowering among older individuals with hypertension, rates of treatment and control are suboptimal. BP control is particularly difficult to achieve in older women. Recent data from the Framingham Heart Study show dramatic reductions in BP control (to goal levels < 140/90 mm Hg) with age among treated hypertensive patients, particularly among women, in whom control rates declined from 38% in those under the age of 60 years to 28% in those aged 60-79 years, and to 23%

in those over age 80. A number of possibilities have been suggested to account for the poor BP control rates in the elderly, including inadequate intensity of treatment, suboptimal drug regimens, and treatment resistance. The same general rules of treating hypertension apply to the whole hypertensive population. The benefits of treating hypertension in the elderly, including those over 80 are well documented (12,13).

Lifestyle modification

Before initiating drug therapy, non-drug therapies may provide significant benefits. The ability of lifestyle changes to lower BP in the elderly is well documented. In particular, dietary sodium should be moderately restricted to 100 to 120 meq/day, since the pressor effect of sodium excess and the antihypertensive efficacy of sodium restriction progressively increase with age. However, the elderly may ingest more sodium to compensate for a decrease in taste sensitivity.

Drugs

Randomized controlled trials leave little doubt that elderly patients benefit from antihypertensive treatment in terms of reduced cardiovascular morbidity and mortality, irrespective of whether they have systolic–diastolic or isolated systolic hypertension There is clear evidence of benefit in the treatment of hypertension in the elderly, including patients over the age of 80. Benefits in elderly patients have been shown with representative agents from several classes such as diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Emphasis here is on treatment: monotherapy is clearly inadequate for controlling BP and preventing cardiovascular disease outcomes and stroke in many elderly patients. Certain general issues need to be emphasized before considering the choice of antihypertensive drugs and the goal blood pressure.

1. Initial doses should be lower (approximately one-half that in younger patients) to minimize the risk of side effects.
2. Reduction in BP should be gradual to minimize the risk of ischemic symptoms; particularly in patients with postural hypotension. Even more caution is advised in the very old, although the benefits from careful

therapy probably outweigh the risks in these patients.

3. The trials on hypertension in the elderly have been performed in relatively fit patients. Greater caution should be applied to the therapy of frail patients, and treatment may be withheld if postural hypotension is a problem, found in as many as 30 percent of elderly patients with systolic hypertension. As a result, careful assessment and management of these problems must be provided before treatment of the hypertension

Diuretics

Low-dose thiazide therapy is the preferred initial treatment for elderly hypertensive and isolated systolic hypertension. It has the advantages of low cost, efficacy, and proven benefit .Low dose thiazide-type diuretics are chosen because of their efficacy in preventing stroke and cardiovascular events and their low cost (14,15). However, questions have been raised about dosing and about the long-term consequences of their adverse metabolic effects. Diuretic therapy increases the incidence of hypokalemia, insulin resistance, and type 2 diabetes.

Calcium channel Blockers (CCB)

The Syst-Eur trial (16), the STONE trial from Shanghai (17), and the Syst-China trial (18) suggest that long-acting calcium channel blockers are also effective in this group of patients. These agents have performed particularly well in preventing stroke in elderly hypertensives. CCBs are metabolically neutral and, except for peripheral edema, are relatively free of adverse effects. In principle, the lack of adverse metabolic effects may represent a major advantage of CCBs over diuretics for a population in which the metabolic syndrome/insulin resistance is becoming epidemic. On the basis of BP-lowering efficacy and outcomes data, CCBs are acceptable alternatives to diuretics for first-line treatment of hypertension in the elderly and may offer advantages in some patient groups, eg, those with the metabolic syndrome.

ACE Inhibitors and ARBs

These antihypertensive drug classes have outcome advantages for patients with concomitant cardiovascular diseases, diabetes with albuminuria, or chronic kidney disease, the "compelling indications" delineated in JNC 7 (14). When administered alone or in combination with other antihypertensive drugs,

ACE inhibitors and ARBs reduce the incidence of new-onset diabetes by about 25% compared with other active treatments, a clear advantage in the elderly. Further, except for ACE inhibitor-induced cough, they are better tolerated than other drug classes. However, these agents have less robust BP-lowering effects than CCBs and diuretics in the elderly, likely because of their volume-expanded/renin-suppressed state. They are most useful in combination therapy with a diuretic or CCB.

Other Drug Classes

Beta-blockers, adrenergic blockers, centrally acting agents, direct vasodilators, and mineralocorticoid (aldosterone) receptor antagonists are useful in lowering BP and in treating some forms of target organ damage/concomitant conditions in elderly hypertensives (15). However, these drug classes lack outcomes data to support their use as first-line treatment of uncomplicated hypertension in the elderly.

Effects of treatment on Dementia

A substudy of the Hypertension in the Very Elderly Trial (HYVET) and other studies (19-21) has reported a modest reduction in cases of incident dementia with blood-pressure lowering treatment. Also another important finding of HYVET-COG is that antihypertensive treatment did not increase the risk of dementia or cognitive decline (22). This contrasts with "the commonly held belief among many doctors that treatment of hypertension in the very elderly might have negative effects on brain function via a reduction in cerebral blood flow (23). In a press release related to the results of HYVET-COG, the UK Alzheimer's Society said that new research shows that hypertension is associated with a 6-fold increased risk of vascular dementia.

Goal blood pressure

Recommended general goals for the treatment of hypertension in the elderly include a diastolic pressure of 85 to 90 mm Hg in patients with diastolic hypertension, a systolic pressure <140 mm Hg except, perhaps, in patients with isolated systolic hypertension. Lower goals have been recommended in hypertensive patients with diabetes mellitus, chronic kidney disease, and coronary artery disease. A concern in elderly patients with isolated systolic hypertension has been that the low diastolic pressure after therapy may interfere with tissue perfusion and adversely affect outcome

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Evolving Clinical Practice Guidelines in the Management of Hypertension

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Abstract

Hypertension is the commonest cardiovascular disease. The prevalence in our country is around 20-22% of adult population. Most patients are treated by general physicians and only around 5-10% of patients need to be referred to specialised centres. Clinical practice guidelines are important so as to guide physicians regarding measurement techniques, clinical and laboratory evaluation and treatment strategies of these patients. Emphasis on non pharmacological life style modification needs to be placed. Since five-six class of drugs are available and a pertinent choice has to be made by the physician, drug pharmacology and interactions need to be known.

Definition and treatment of hypertension have been evolving over last 5-6 decades and various medical bodies have been updating the guidelines. The JNC guidelines (I-VII) have been the most followed ones. The British guidelines, European Society and WHO guidelines are also useful documents. Our own Indian guidelines have been published in 2000 and 2007. Hypertension is not only a disease due to genetic predisposition but psychosocial, environmental and dietary factors have important implications. Individuals from different races have variation in the pattern of disease. Thus, guidelines need to be evolved by various countries which are suitable for their physicians and countrymen.

Key Words : Hypertension, clinical practice guidelines, psychosocial and environmental factors, dietary factors

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Hypertension is the commonest cardiovascular disease in our country & world over. About 25% of world population above 30 years has hypertension. Hypertensive patients have increased risk of coronary heart disease (CHD), cerebrovascular accidents (hemorrhagic & occlusive), heart failure, atrial fibrillation, chronic renal failure, eye changes, aortic aneurysms, aortic dissections & peripheral arterial disease. Antihypertensive treatment brings back the risk to near normal although it does not reach the level of normotensive individuals. It is associated with a major reduction in the risk of fatal or non-fatal stroke (about 30–40%), but, coronary events are reduced to a lesser degree (20%). There is also a large reduction in the incidence of heart failure and other risks involved. Doctors from all fields especially primary care physicians are expected to treat most patients of hypertension & only 5-10% of patients need to be referred to specialists.

Clinical practice guidelines need to be evolved so as to provide simplistic guidelines to physicians regarding measurement, clinical evaluation, risk stratification, baseline investigations and pharmacotherapy. At present there are guidelines for management of hypertension from the British Hypertension Society (BHS) (1), World Health Organization - International Society of Hypertension (WHO-ISH) (2), European Society of Cardiology (3), the Joint National Committee (JNC VII) (4) guidelines from USA & also the Australian (5) & Japanese guidelines. These guidelines provide statistical data and practice suggestions according to the population of their countries. We have our own Indian hypertension guidelines I & II (6), which were released in the year 2000 and 2007 respectively. These are the joint guidelines of Association of Physicians of India, Indian Hypertension Society, Cardiological Society of India and Indian Medical Association.

With evolution of concepts in management of hypertension most bodies have been updating the guidelines, every 4-5 years to guide physicians (BHS 1989, 1993, 1999 and 2004). It is important to review all the guidelines so as to look at the interpretation of data by different experts.

In mid 90's the definition of hypertension was different in different

guidelines with WHO guidelines having 160/95 & JNC V having 140/90 as cut off levels. Now there is uniformity in the cut off levels in all guidelines which is 140/90. New terms like optimal BP <120/80 & normal BP 120-129/80-84 mm Hg have been introduced by most bodies. A category of high normal is included by Indian & BHS guidelines corresponding to 130-139/85-89 mm of Hg. The JNC VII has used the term pre hypertension for this category. This term however has not been picked up by other guidelines because even in the Framingham study although the risk of developing hypertension was higher in subjects with high normal (130–39/ 85–89mm Hg) than in those with normal blood pressure (120–129/80–84mm Hg) but for the layman, the term "prehypertension" may create anxiety and will result in unnecessary medical visits and examinations in many subjects.. The JNC VII recognizes stage I & II hypertension, while the Indian guidelines hold on to the stage I, II, & III of hypertension, as was the case in JNC VI.

In blood pressure measurement electronic equipments that are semi automatic have been discouraged by most guidelines (BHS, Indian). The Mercury sphygmomanometer is considered the gold standard. Ambulatory BP monitoring is recommended in only some special situations and not as a routine. It is particularly considered when considerable variability of office BP is found over the same or different visits (marked discrepancy), resistance to drug treatment is suspected, hypotensive episodes are suspected usually in elderly and diabetic patients or elevated office BP is suspected in pregnant women and pre-eclampsia.

Initially the guidelines (early 90's) used primarily diastolic blood pressure for treatment decisions. More recently systolic BP is recognized as an equally or even more important factor after the release of the SHEP trial (7) and SYS-EUR trial results (8). In SHEP trial, individuals (aged= 60 years) with isolated systolic hypertension, antihypertensive treatment with low-dose chlorthalidone reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Similarly major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000. In the Syst-Eur trial (Syst-Eur 1), 4695 ISH patients aged >

60 years were treated with nitrendipine 10-40 mg daily, with the possible addition of enalapril and hydrochlorothiazide. At a median follow-up of 2 years, the incidence of stroke was reduced by approximately 42% and cardiovascular endpoints by 31% in the active treatment group. Now the value of pulse pressure as prognostic factor is being realized.

Along with the, level of blood pressure, the overall risk of the individual is important for initiation of drugs and level of control to be achieved. The concomitant risk factors (diabetes, dyslipidemia, metabolic syndrome) and target organ damage need to be considered for these. The target BP is discussed in most guidelines and the level is 140/90 in most individuals. In diabetics & high risk individuals (stroke, renal dysfunction, proteinuria) the target blood pressure in most guidelines is < 130/80 mm of Hg. The beneficial effect (reduction in macro and microvascular complications) of a greater versus a smaller blood pressure reduction in type 2 diabetic patients was demonstrated by the HOT (9) and UKPDS trials and confirmed by the ABCD studies. HOT study (9) confirmed that there was no increase in cardiovascular risk in patients randomized to the lowest target blood pressure group. The earlier suggested "J" shaped curve by Cruickshank is not believed in any more.

There are expectedly some differences between the various guidelines. Indian guidelines emphasize the salt content of Indian food items, which is highly relevant to our country because of high usage of salt. Such charts are not available in any other guidelines. Similarly Indian guidelines state that alcohol abstinence is preferred. This is because of increased prevalence of problem drinking in India and lack of randomized data suggesting protective effects of alcohol. The Indian guidelines further highlight the metabolic syndrome according to our race since the criteria for central obesity as per waist circumference are different in different races.

The lifestyle measures that are widely agreed to lower blood pressure or cardiovascular risk, and that should be considered in all patients are: 1) smoking cessation, 2) Weight reduction in the overweight (JNC VII maintains target BMI <25 while Indian guidelines

suggest <23 Kg/m^2), 3) moderation of alcohol consumption, (according to ESC 2007 hypertensive individuals who drink alcohol should be advised to limit their consumption to no more than 20–30 g ethanol per day for men, and 10–20 g for women), 4) Physical activity (primarily endurance physical activity like walking, jogging, swimming), 5) Reduction of salt intake (The recommended adequate daily sodium intake has been recently reduced by ESC in 2007 from 100 to 65mmol/day corresponding to 3.8 g/day of sodium chloride, which may be currently difficult to achieve while both Indian and JNC VII maintain daily salt intake <100 mmol/day or < 6 g/day of sodium chloride), and 6) healthy diet such as increase in fruit and vegetable intake and decrease in saturated and total fat intake (fruits and vegetables 4–5 servings or 300 grams of vegetables per day), along with increase in fish and potassium intake.

There have been significant changes in the drug treatment of hypertension. The initial JNC I-IV had "stepped care approach" in which the treatment algorithm was compartmentalized & physicians were guided regarding step I and step II drugs. Recent guidelines likes JNC V-VII have emphasized on "individualized care approach" for drug therapy of hypertension. Five classes of agents have been included in the 1st step thus allowing greater discretion to physicians. Beta-blockers and diuretics are earlier drugs & most trials in 80's & 90's were evaluating these two groups. The agents are now grouped as conventional agents. The angiotensin converting enzyme inhibitors (ACEIs) and calcium channel blockers were added in 80's & are considered as newer agents. In the early 90's most guidelines included ACEIs, calcium channel blockers, beta-blockers and diuretics as 1st line agents. In the late 90's Alpha blockers were also added as 1st line agents. However, after the ALLHAT trial (10) alpha blockers have been withdrawn as 1st line agents. Recently angiotensin receptor blockers (ARBs) have been included as 1st line agents along with the four earlier mentioned groups. The most recent ONTARGET trial (11) proved that ARBs were equivalent to ACEIs in patient with vascular disease or high risk diabetes. The combination of ACE-inhibitors and ARBs was associated with the more adverse events without an increase in benefit when compared to either agent

used in full dose. As a result the concept of using complete RAAS blockade in treatment of hypertension is fading.

Even more recently, based on some reviews beta-blockers are being withdrawn as 1st line agents. LIFE study showed that losartan compared to beta-blocker (Atenolol) over 5 yrs of follow up had a significant, 13% reduction in major cardiovascular events (the primary end point) and a 25% difference in the incidence of stroke. This was considered strongly by BHS guidelines & now other bodies are following the same.

There is now realization of different hemodynamic profile of hypertensives according to the age. The young have high renin activity and more sympathetic drive and the old have low renin activity, stiffer vessels and more blood volume. So ACE I's & ARBs are preferred in the young & calcium channel blockers & diuretics are preferred in the elderly population. Beta blockers may still be used in young but should be avoided in elderly unless there are other compelling reasons like angina or heart failure. Drug treatment in elderly can be initiated with thiazide diuretics and /or calcium antagonists. Trials specifically addressing treatment of isolated systolic hypertension, a particular problem in elderly, have shown the benefit of thiazides and calcium antagonists but subanalysis of other trials also show efficacy of angiotensin receptor antagonists. Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects. BP goal is the same as in younger patients, i.e. <140/90mm Hg or below, if tolerated. Many elderly patients need two or more drugs to control blood pressure and reductions to <140mm Hg systolic may be particularly difficult to obtain. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture. In subjects aged 80 years and over, evidence for benefits of antihypertensive treatment was inconclusive. However, recently the HYVET study (12) published in 2008 has provided evidence that antihypertensive treatment with indapamide (sustained release), with or without perindropril, in persons 80 years of age or older is beneficial with respect to fatal and nonfatal stroke, death from any cause, death from cardiovascular cause and rate of heart failure.

A significant change in the guidelines more recently is acceptance of fixed dose combination for treatment of hypertension. Drugs from different classes have synergistic effects and compliance is an important issue. The BHS and Indian guidelines both endorse combinations of drugs with synergistic effect. Most guidelines now provide data regarding good combinations (CCB's + ACE I's, ACE I's + diuretics, ARBs + CCB's) and bad combinations (ACE I's + ARBs, beta blockers + ACE I's, CCB's + diuretics). The blood pressure lowering arm of ASCOT trial (ASCOT-BPLA) showed that amlodipine combined with perindopril had better cardiovascular end points and total mortality compared to combination of atenolol and diuretic over 100,000 patient years of observation (stroke decreased by 23%, all cause death by 11%, cardiovascular events by 16% and new onset diabetes by 30%). Beta blockers especially in combination with a

	Indian HTN Guidelines II	ESC 2007	BHS IV	JNC VII	AUSTRALIAN GUIDELINES 2008
1. Classification					
<120/80	Optimal	Optimal	Optimal	Normal	Normal
102-129/80-84	Normal	Normal	Normal	Prehypertasion	High Normal
130-139/85-89	High Normal	High Normal	High Normal		
140-159/90-99	Stage I	Stage I	Stage I	Stage I	Grade I (mild)
160-179/100-109	Stage II	Stage II	Stage II	Stage II	Grade II (mod)
≥ 180/110	Stage III	Stage III	Stage III		Grade III (severe)
ISH G – I	SBP 140-159 DBP < 90	SBP >140 DBP < 90	SBP 140-159 DBP < 90	SBP > 140 DBP < 90	SBP ≥ 140 DBP < 90
ISH G – II	SBP ≥ 160 DBP < 90		SBP ≥ 160 DBP < 90		SBP ≥ 160 DPB < 70
2. Lifestyle Changes					
Wt reduction	Targat BM I <23 kg/ m²	Wt stabalisation	Target BM I 20 -25 kg/ m²	Target 18.5–24.9 kg/m²	<25 kg/m²
Sodium restriction	<100 mmol/day	<65 mmol/day	<100 mmol/day	<100 mmol/day	<65 mmol/day
Alcohol consumption	≤ 60ml/day in men ≤ 30ml/day in women Abstinence preferred	20 – 30g /day in men 10 – 20 g/day in women	<3 units/day in men <2 /day in women	<2 drink/day in men <1 drink/day in women	<2 drink/day in men <1 drink/day in women

	Indian HTN Guidelines II	ESC 2007	BHS IV	JNC VII	AUSTRALIAN GUIDELINES 2008
3. Goals of Treatment					
	Young < 130/85 Elders < 140/90 Stroke < 130/85	All pt.<140/90	Optimally treated < 140/85 Audit standard < 150/90	All pt. < 140/90	All pt. < 140/90 or lower if tolerated proteinuria >1g/day <125/75
	Diabetes < 130/80	**Diabetes or high risk** < 130/80	**Diabetes** : optimally treated <130/80 audit standard < 140/80	**Diabetes or renal disease** < 130/80	**Diabetes or high risk** <130/80
4. 1st line Drug					
	Low dose diuretic In case of compelling indications – CCBs, ACEIs, ARBs, Beta Blockers	Five classes :– thiazides, CCBs, ACEIs, ARBs, Beta Blockers	<55 yr ACEIs or Beta Blockers >55 yr CCBs or diuretic	Thiazides	Three classes :- ACEIs, ARBs, CCBs
5. Treatment of Elderly					
	Low dose diuretic or CCBs	Thiazides CCBs, ARBs, ACEIs, Beta Blockers	Low dose diuretic or CCB's	Low dose diuretic	Four classes :- ACEIs, ARBs, CCBs, Thiazides
6. Hypertension in Pregnancy					
Treatment threshold	—	≥ 140/90	>150-160/100-110	>150-160/100-110	
Drugs of choice	Methyl dopa (1st line) CCB's, beta blockers, labetelol, alpha blockers	Methyl dopa, CCBs, beta blockers, labetelol	Methyl dopa, CCBs (nifedipine)	Methyl dopa, CCBs, beta blockers, labetelol, clonidine	

thiazide diuretic should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.

Research in hypertension is an ongoing process. We are still looking at the ideal drug & drug combination. The target level of BP is likely to come down since there is a continuous relationship between the level of blood pressure and the risk of complications. Starting at 115/75 mm Hg cardiovascular disease risk doubles with each increment of 20/10 mm Hg throughout the blood pressure range. Newer agents like renin antagonist (aliskiren) are likely to be used clinically. The benefits of some combinations over others will be delineated. Some high risk individuals requiring better blood pressure control will be defined. Consequently with our greater understanding of mechanism of

hypertension and translation of risk reduction trials into practice guidelines we can expect ongoing changes in various guidelines.

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National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases (CVDs) and Stroke

Focus on: Integrated strategies for prevention and control of hypertension at the level of primary and secondary health care

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Abstract

Globally, Non-Communicable Diseases (NCDs) are increasingly recognized as a major cause of morbidity and mortality. NCDs are also assuming alarming proportions in the South-East Asia Region (SEAR). India too is experiencing a rapid epidemiological transition, with a large and rising burden of chronic diseases, which were estimated to account for 53% of all deaths and 44% of Disability Adjusted Life Years (DALYs) lost in 2005. From the estimates of Diabetes, CVDs and Stroke in India, it emerges that the highest number of cases in India are due to Diabetes, highest DALYs lost due to Ischaemic Heart Disease (IHD) and the highest number of Years of Life Lost (YLL) as well as deaths are due to Stroke. The burden of cardiovascular diseases is rising in India, besides the maximum number of cases, it may become the largest cause of death and disability by 2015. The advancing NCDs are propelled by demographic, economic and social factors. The common risk factors are physical inactivity, obesity, raised blood pressure, tobacco use, alcohol consumption, low fruit and vegetable intake, raised cholesterol and glucose and hence the population prevalence levels of these factors can predict the future disease burden. The NCDs do not have a linear causality but have a 'web of causation' with complex interrelationships among various factors. The risk factors and the

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interventions for the prevention and control of Diabetes, CVDs and Stroke are somewhat common and thus, concerted efforts for prevention and control are worth. The need is to institute priority interventions aimed at reducing the burden of NCDs through setting up a newer national non communicable diseases programme. This involves setting up surveillance systems based on risk factors; strategy for tobacco control, diet, physical activity and health; capacity building of health personnel; primary and secondary prevention of all risk factors and ensuring availability of cost effective investigations, medications/interventions and follow up. A National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke has already been launched on 4th January, 2008 on a pilot basis.

Key Words : Non communicable diseases, Disability adjusted life years, diabetes, cardiovascular diseases, stroke

Introduction

Globally, non communicable diseases (NCDs) are increasingly recognized as a major cause of morbidity and mortality. The World Health Report 2004 had indicated that NCDs account for almost 60% of deaths and 47% of the global burden of disease. Seventy-five per cent of the total deaths due to NCDs occur in developing countries (1).

NCDs are assuming alarming proportions in the South-East Asia Region (SEAR). They account for 51% of all deaths and 44% of the disease burden in the Region. Therefore, NCDs should no longer be regarded as a problem confined to the developed countries and affluent segments of society. In fact they are clearly emerging as a major public health challenge in developing countries where they create a double burden on top of the infectious diseases that still afflict these countries (1).

India is experiencing a rapid epidemiological transition, with a large and rising burden of chronic diseases, which were estimated to account for 53% of all deaths and 44% of Disability Adjusted life Years (DALYs) lost in 2005 (2). In India, non communicable diseases (NCDs), especially Diabetes Mellitus, cardiovascular diseases (CVDs), cancers, stroke and chronic lung diseases have emerged as major public health problems due to an

ageing population and environmentally-driven changes in behaviour (3). Though the term NCDs encompass a plethora of conditions (Table 1), hereon, the term 'Non communicable Diseases (NCDs)' in this paper has been used to refer to Diabetes, Cardiovascular Diseases and Stroke only.

Magnitude of the Problem in India

Estimates of DALYs, YLL, deaths and cases of IHD, stroke and diabetes in India have been shown in Figures 1-3. It emerges that the highest number of cases are due to diabetes, highest DALYs lost due to IHD and the highest number of YLL as well as deaths are due to stroke. The burden of cardiovascular diseases is rising in India, besides the maximum number of cases, it will be the largest cause of death and disability by 2015.

The prevalence of hypertension has been reported to range between 20–40% in urban adults and 12–17% among rural adults (4). High blood pressure has been shown as the leading cause of avoidable mortality and morbidity in all world regions. High blood pressure is a main risk factor for stroke, cardiac failure, renal failure and coronary heart disease (5). Figure 4 depicts the percentage attributable risk due to hypertension for diseases like stroke, myocardial infarction, PVD, cataract and IHD.

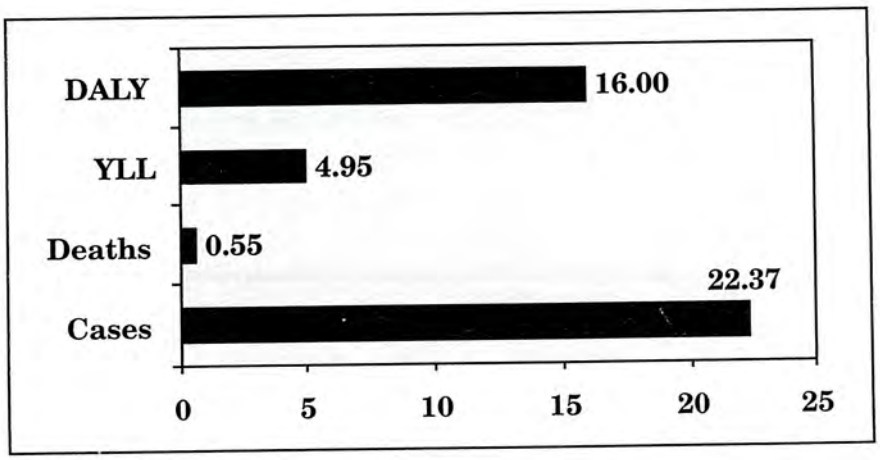
Table 1: Magnitude of Non-Communicable Diseases in India

	2005	2015
Total deaths in India	10,362,000	10,949,000
Deaths from NCDs	5,466,000 (53%)	6,458,000 (59%)
Deaths from major NCDs		
Cancers	826,000	1,069,000
Diabetes	175,000	236,000
Respiratory Diseases	674,000	864,000
Cardiovascular Diseases	2,989,000	3,465,000

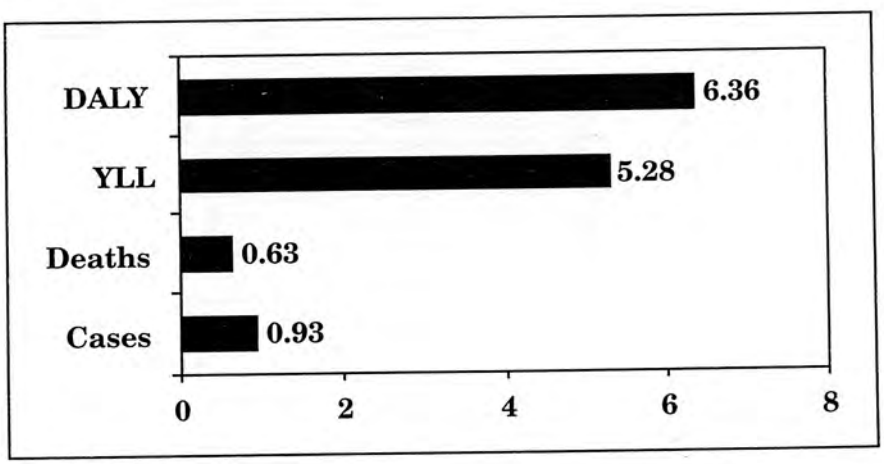
(Non-communicable diseases include neoplasms, endocrine disorders, neuropsychiatric conditions, sense organ diseases, cardiovascular diseases, respiratory diseases, digestive diseases, genitourinary diseases, skin diseases, musculoskeletal diseases, congenital anomalies and oral conditions)
Source: Min. of Health and Family Welfare, GoI

Risk Factors

These advancing epidemics are propelled by demographic, economic, and social factors. Urbanization and industrialization are changing the patterns of living in ways that increase

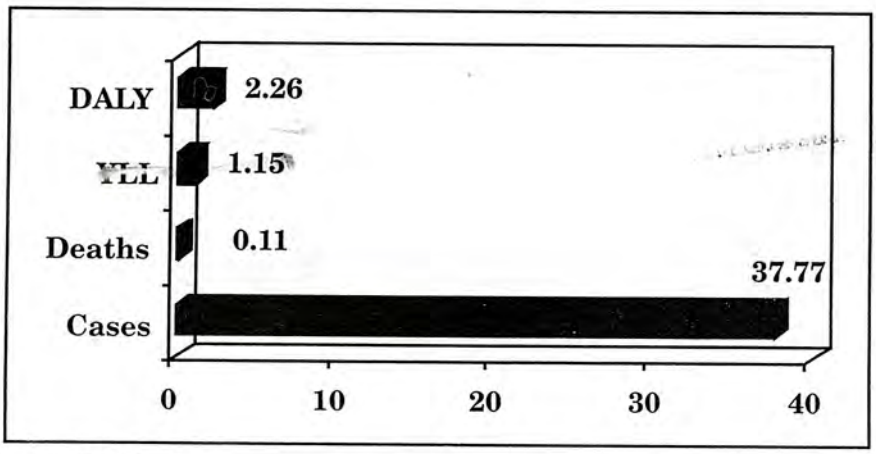


Numbers in Millions
DALY- Disability adjusted life years; YLL- Years of life lost
Source: Assessment of burden of non-communicable diseases in India, www.whoindia.org
Figure 1: Burden of IHD in India (2004)

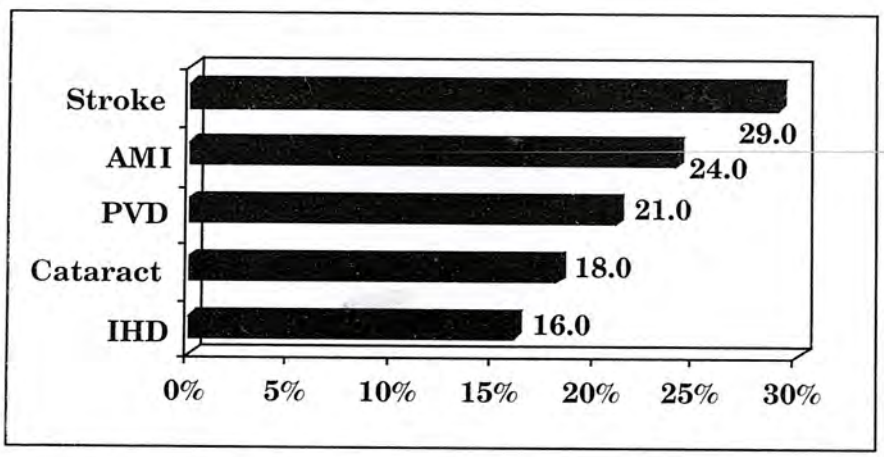


Numbers in Millions
DALY- Disability adjusted life years; YLL- Years of life lost
Source: Assessment of burden of non-communicable diseases in India, www.whoindia.org
Figure 2: Burden of Stroke in India (2004)

behavioural and biological risk factor levels in the population. Substantial variations exist between different States, but risk levels are rising across the country, most notably in urban areas of demographically and



Numbers in Millions
DALY- Disability adjusted life years; YLL- Years of life lost
Source: Assessment of burden of non-communicable diseases in India, www.whoindia.org
Figure 3: Burden of Diabetes in India (2004)



AMI – Acute myocardial infarction; PVD – Peripheral vascular disease; IHD – Ischaemic heart disease
Source: Assessment of burden of non-communicable diseases in India, www.whoindia.org
Figure 4: Percentage Attributable Risk due to Hypertension (2004)

economically more advanced States of India. Nationally representative distribution data are not available for all risk factors. Several community-based surveys, done in different parts of India at different times, have contributed to a patchwork profile of risk in segments of the population (3). Table 2 shows prevalence of some of the known risk factors.

The common risk factors are tobacco use, alcohol consumption, low fruit and vegetable intake, physical inactivity, obesity, raised blood pressure, raised cholesterol and glucose and hence the population prevalence levels of these factors can predict the future disease burden. The NCDs do not have a linear causality but have a 'web of causation' with complex interrelationships among various factors. To illustrate, web of causation for CVDs has been depicted in Figure 5.

Levels of awareness, treatment, and adequate control are low for hypertension, diabetes, and dyslipidaemia, especially in rural areas (6). With advancing health transition, the poor are increasingly affected by chronic diseases and their risk factors. Low levels of education and income

Table 2 : Prevalence of Risk Factors in India

S.No.	Risk Factor	Prevalence
1.	Tobacco (all forms)	11 % (females), 57 % (males)*
2.	High Blood pressure	164.2 per 1000 (urban), 157.4 per 1000 (rural)#
3.	Veg and Fruit Intake	50 % daily (15-64 years)**
4.	Physical Inactivity	60-80 % Sedentary**
5.	Dyslipidaemia	37.5 % (15-64 yrs), 62 % (industrial workers)•
6.	Obesity	14.8 % (females), 12.1 % (males) *
7.	Alcohol	Range: 7 % (Gujarat) to 71 % (Arunachal Pradesh)##

* NFHS – 3, 2005-06, IIPS.

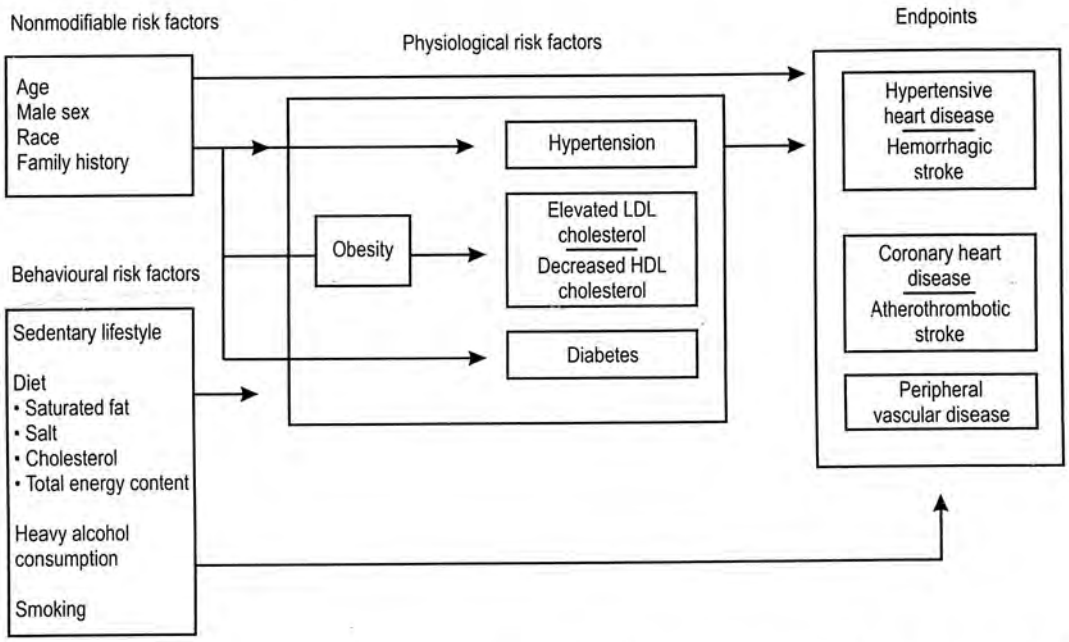
http://www.whoindia.org/LinkFiles/Assessment_of_Burden_of_NCD Updated.pdf.

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##http://www.ias.org.uk/resources/publications/theglobe/globe200502/gl200502_p7.html

now predict not only higher levels of tobacco consumption, but also increased risk of coronary heart disease (7). Urban slums also have high rates of diabetes and dyslipidaemia (8).



Source: Wong ND, Black HR and Gardin JM, Preventive cardiology: a practical approach, Chicago, McGraw-Hill, 2005.

Figure 5: Web of Causation for Cardio Vascular Diseases (CVDs)

Are Concerted Efforts for Prevention and Control Really Worth?

Interventions for chronic disease prevention and health promotion have been tried and tested. Systematic reviews have evaluated the available evidence on the effectiveness of these interventions and a wide range of interventions at the community, population and macroeconomic level and have been found these to be effective (9).

There is evidence based information that NCDs are preventable through integrated and comprehensive interventions. The most successful ones have employed a range of population wide approaches combined with interventions for the individuals. WHO estimates that an additional 2% annual reduction in

chronic disease death rates in India over the next 10 years would result in an economic gain of 15 billion dollars for the country. At least 80% of premature heart disease, stroke and type 2 Diabetes and 40% of cancers could be prevented through avoidance of tobacco products and the adoption of healthy diets and regular physical activity (10).

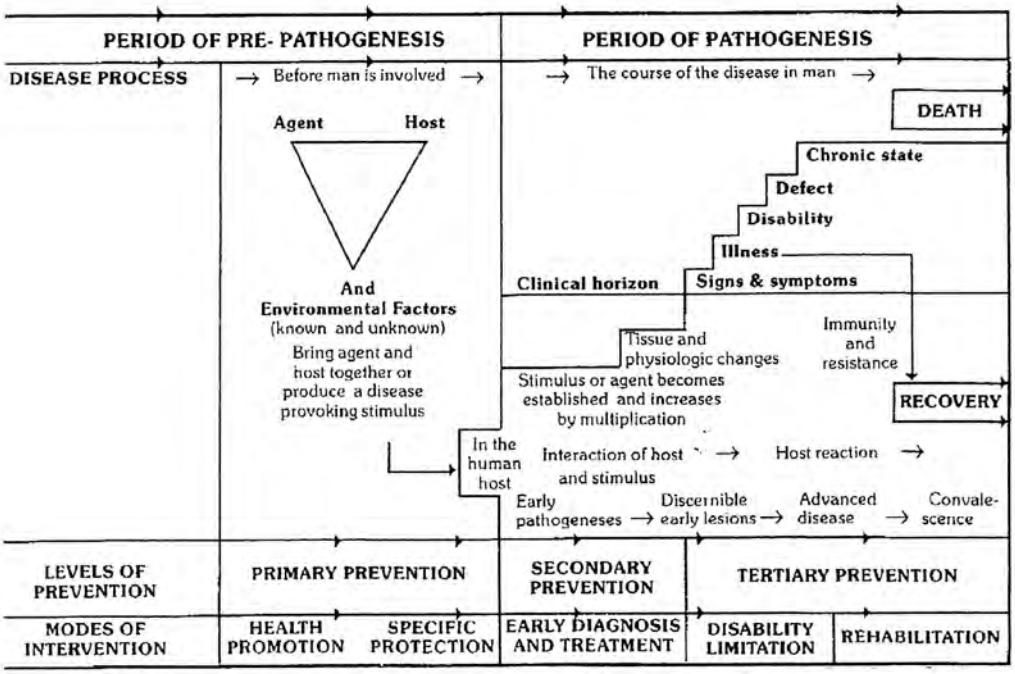
Way Forward

The population-wide application of existing knowledge has the potential to make a major, rapid and cost-effective contribution to their prevention and control and to benefit all segments of the population. The main issue for policy-makers, at all levels of public health in India, is how to deal with the growing burden of non communicable diseases in the presence of persisting communicable diseases. Furthermore, this challenge must be faced even when health system resources are already inadequate. Although considerable policy gains can be made very cheaply, especially inter-sectoral, extra provision must be found. This requires a greater share of national resources for health care, better use of existing resources, and new sources of funding.

One of the most exciting possibilities to emerge in public health in recent years is the integration of communicable and non communicable diseases prevention and control into comprehensive health systems led by primary care. Bringing this to fruition will mean reshaping the future of primary health care in response to a changing world. It would see all patients being offered – across their lifespan – prevention, treatment and long-term management of both sides of the double burden. Achieving such integration will not be easy, but efforts need to be done in this direction. A continuum of care for all diseases should be available to the community (Figure 6).

Priority interventions aimed at reducing the burden of NCDs include setting up national non communicable diseases programmes which include: setting up surveillance systems based on risk factors; capacity building of health personnel; ensuring availability of cost effective medications; implementing the Framework Convention for Tobacco Control and the Global Strategy on Diet, Physical Activity and Health; and incorporating both primary and secondary prevention of all risk factors.

The recognition of behavioral risk factors like tobacco, physical inactivity, and unhealthy diets can no longer be ignored and the realization that



Source: Leavell H R, Clark E G (1965). Preventive Medicine for the Doctor in his Community. McGraw-Hill, New York.

Figure 6: Natural History of Disease and Levels of Prevention

biological risk factors like blood pressure, diabetes, and dyslipidemia need to be appropriately and adequately controlled have at last opened the strategic pathways for CHD prevention and control in India (11). The Government of India had been planning for a national programme for quite some time and a pilot programme was formally launched on 4th Jan 2008 (12).

The Intervention / Programme

General Principles regarding strategies and approaches at various levels of prevention have been shown in Table 3.

Design of the Programme

It is necessary to integrate the interventions with the existing programmes for communicable and non communicable diseases without creating any new vertical structures below the district level.

Objectives

- Primary prevention of major NCDs through health promotion

Table 3: Strategies, Approaches and Target Population at various levels of Prevention

Level of Prevention	Target Population	Strategy	Approach
Primordial	General Population	Avoiding the development of 'risk factors' (*Preventing hypertension by measures aimed at reducing the blood pressure levels in the population as a whole)*	Avoid 'risk behaviour'; Policy measures for preventing exposure to 'risk factors'
Primary	Healthy individuals 'at risk'	Reducing the 'risk factors' with or without interventions to prevent clinically manifest disease (*Early identification and effective management of individuals who are 'at risk' of hypertension, e.g. individuals with obesity, genetic* predisposition, stressful life styles).	Modify established risk behaviour and risk factors; Specific interventions
Secondary	Individuals with disease (diagnosed / undiagnosed)	Early detection and appropriate management; Modifying the 'risk factors' (*Identification and management of hypertensive individuals, with / without manifestation of end organ disease, to reduce the morbidity and mortality)*	Use of drugs and/ or changes in lifestyle
Tertiary	Individuals with diagnosed disease	Modifying the 'risk factors'; Appropriate management and follow up (Disability limitation and rehabilitation of those already suffered from any of the consequences of hypertension like stroke, etc)	Use of drugs and/ or changes in lifestyle; Rehabilitation

- Surveillance of NCDs and their risk factors in the population
- Capacity enhancement of health professionals and health systems for diagnosis and appropriate management of NCDs and their risk factors
- Reduction of risk factors in the population
- Establishment of National guidelines for management of NCDs
- Development of strategies and policies for prevention by inter-sectoral coordination
- Community empowerment for prevention of NCDs

Strategies

An integrated programme will provide screening and targeted interventions so as to reduce the mortality and morbidity due to NCDs. The programme interventions have to be a judicious mix of targeting those at high risk as well as the general population.

1. Health Promotion/ Health Education (targeting general population)

It is well proven that the risk of developing NCDs may be prevented by adopting healthy life styles, healthy diet and physical activity. This could only be achieved through sustained IEC Campaign targeting healthy risk free populations through development of an effective communication strategy, organizing awareness and sensitization camps, using electronic, print and various other methods so that individual, group and community behaviour can be modified. Therefore emphasis needs to be laid on IEC at all levels.

The IEC should be strengthened for community awareness. This has to go hand in hand with interventions at specific settings like worksites, schools, rural, urban and peri-urban areas. The health education also needs to be targeted, which means it should be specifically designed for and delivered to well- defined target groups such as children, women and industrial employees. This should be carried out in the true spirit of community participation involving civil society partners and others (NGOs, school health committees, RWAs, VHSCs, ASHAs, SHGs, employees unions, etc.) to enable the early initiation and effective implementation of such programmes. The IEC campaigns could use iconic figures from various fields and also utilise TV sitcoms. Few of the interventions are:

i. Community Based Interventions

In addition to IEC, the focus of the interventions would be on behaviour change through: (a) changing dietary habits viz. improving intake of fresh fruits and vegetables, whole grain and pulses, avoidance of refined, processed and preserved food, control intake of salt and sugar, restrict fat to 15-20% of the calories consumed, avoid hydrogenated oils/ vanaspati, increase intake of fibers in the diet, etc.; (b) increasing physical activity through walking, sports, exercise, etc.; (c) avoidance of tobacco and alcohol; (d) stress management, etc.

ii. Targeted Interventions

(a) Workplace Interventions

To promote healthy workplaces through informal / formal sessions involving health talks, facilitation for lifestyle change, health check-ups and screenings for those at risk with follow up counseling.

(b) School Based Interventions

To promote healthy habits, proper diet, physical activity and bring health promotion as a defined agenda in the school curriculum.

2. Reorienting Public Health Delivery system and Professional Education

The public health system has to be reoriented and strengthened at the primary and secondary level by strengthening, mobilizing and training health care providers to involve in risk detection and screening viz. blood pressure checks, recommending lifestyle modifications, dissemination of information and referring for further management. These activities need to be carried out at the time of joining as well as periodically by Continuing Medical Education.

3. Diagnosis and Management (targeting those at high risk)

Targeting people who suffer from elevated risks demonstrated through hypertension, overweight/obesity, low levels of physical activity, high blood lipid and glucose levels and those who have suffered from a previous cerebral or coronary event and are at the highest risk is possible through:

i. Opportunistic screening of persons at the point of primary contact with any health care provider would involve simple clinical examination comprising relevant questions and easily conducted physical measurements (such as history of tobacco

consumption and measurement of blood pressure, etc). To begin with, this could be started in the organised sector, CGHS and Railways. This experience can then be used to upscale efforts in the public health system. For this, context specific training needs to be imparted to health care providers including non-physician health care providers like nurses and multi-purpose workers, which will enhance their knowledge, skills and motivation for conducting such opportunistic screening regularly.

ii. **Targeted screening** should be planned by development of context-specific algorithms for risk detection, stratification and management, in persons who are considered to be at high risk during the initial opportunistic screening. This needs to be complemented by provision of appropriate investigation services at primary/secondary levels of care.

The programme should integrate essential elements of acute as well as chronic health care for NCDs at primary and secondary health care levels, along with strengthening of referral mechanisms. This would require strengthening of health infrastructure for NCD care facilities including equipment and drugs at all levels of health care.

Interventions aimed are early diagnosis and appropriate management through following:

i. Setting up special clinics

Special clinics for NCDs should be established at the District Hospital. The clinic should do the screening, provide management (based on standard treatment guidelines) and appropriate referral to tertiary care centre or the nearby Medical College.

ii. Appropriate technology use

The high cost, low yield technologies need to be replaced with cost effective interventions, both in public as well as private sector.

iii. Specific interventions at tertiary level

Referral centres need to be identified. Medical colleges can be upgraded to serve as tertiary care referral centres providing quality services in NCD care (prevention, control, management) in general and Diabetes, CVDs, Stroke in particular. In addition, they can also be used for developing human resources in the concerned specialty.

4. Social Mobilization and Community Participation

The community based organizations (CBOs), local leaders and opinion influencers, local NGOs need to be involved along with the District administration for promotion of healthy lifestyles and prevention of NCDs. Involvement of local health workers for IEC, prevention, early detection and appropriate referral has to be ensured. Strengthening the capacity for care by self, family, community, paramedic, or traditional healer obviates the need for frequent revisits to secondary and tertiary care providers, and may ensure a sustainable system (13).

5. Research and Assessment

The research areas could include qualitative and quantitative research to study risk factors and their determinants, effectiveness/ cost-effectiveness of community based programmes to promote health behaviours, and feasibility of integration into National Rural Health Mission, to name a few.

Population based studies are required to assess the prevalence of risk factors in order to study the distribution of risk factors for non communicable diseases especially diabetes, CVD and stroke. This will include assessment of: demographic and socio-economic characteristics; tobacco/alcohol use; physical activity; dietary patterns; BMI and waist circumference measurements; blood pressure; and blood glucose and lipids, to list a few. This information will also be helpful in monitoring, evaluation and feedback.

6. Policy Issues

At the National level, planning of the programme should be such that it is integrated in the existing efforts and is a part of the health system without creation of new structures. The existing IEC efforts need to be bolstered and made comprehensive. Policy guidelines and regulation need to be enforced regarding salt content in processed foods, tobacco and alcohol as well as junk food advertisements, etc.

7. Programme Delivery

The programme should be integrated as part of District Health Society set up under the NRHM. A nodal officer can coordinate the implementation of various activities for the programme and report to the District Health Society. At the State level, a nodal officer could be earmarked as a part of the State

Health Society. A NCD Cell at the Centre should be established to plan, coordinate, and monitor the activities at National and State level. It should obtain database from the integrated HMIS for effective monitoring, evaluation and feedback. It should also be involved in policy decisions like regulation of quantity of salt in processed foods, strategies to reduce tobacco and alcohol consumption, etc.

Hypertension Prevention and Control Activities at Primary And Secondary Levels

High blood pressure is a major risk factor for CHD and stroke and its control has been shown to be a major determinant of improved survival in diabetics. Hypertension control programme should be a part of a comprehensive strategy for the reduction of total cardiac risk. It should include control of other major risk factors like smoking, hypercholesterolemia, diabetes, obesity, etc. Interventions specific to hypertension have been listed below.

Primordial Prevention

Community or population-based strategies for prevention of hypertension include the following:

(i) Awareness that high blood pressure is a health problem and as such yearly measurement of blood pressure starting from the age of 30 years should become a standard procedure.

(ii) Modify diet to reduce the salt intake as much as possible and increase food intake of items rich in potassium.

(iii) Cultivate the habit of regular physical exercise, which helps in keeping the blood pressure low.

(iv) Control of dietary fat intake-especially saturated fats – and exercise to maintain normal weight, avoid obesity and hypercholesterolemia.

(v) Avoid excess alcohol since it promotes hypertension.

(vi) Use relaxation techniques like yoga, meditation, getting involved in hobbies like gardening or music, which help in relaxation.

(vii) Avoiding or abstaining from the use of tobacco and stimulants including caffeine, which increase blood pressure.

Primary Prevention

The goal of primary prevention is specially applicable to individuals with a family history of hypertension which may be present in one or both parents.

Essential hypertension has a strong genetic background. In such a setting, it is necessary that the parents should be made aware of the possibility of their children having systemic hypertension. Since good or bad habits are formed in background of hypertension, special attention is directed to prevention right from childhood. Every effort should be made to make children aware of the advantages of good eating habits, regular exercise, abstaining from use of tobacco, avoiding overweight, and getting involved in hobbies with can help in relaxation.

Secondary Prevention

The requirements of secondary prevention consist of:

(i) Identifying hypertensive individuals.

(ii) Instituting non-pharmacological management of hypertension in all.

(iii) Use of appropriate drugs to control the blood pressure.

(iv) Regular follow-up to ensure control of blood pressure and compliance of management.

(v) Evaluation of other cardiovascular risk factors which may co-exist and magnify risk of cardiovascular disease, with appropriate measures for their effective control.

Thus, health care facilities at primary and secondary level, in rural as well as urban areas, need to be strengthened to be able to carry out these activities in addition to other work.

Summary

The expanded mandate of health care, which involves the addition of chronic care to pre-existing services (such as maternal and child, health, population control, and control of infectious diseases), can be delivered only when health care providers of all categories are adequately mobilized and involved at each level of health care and NCD services are integrated into various levels of care (13).

The development of evidence-based, context-specific, and resource-sensitive clinical practice guidelines and their integration into various levels of health care will facilitate greater use of low cost-high impact interventions.

Education and training of health care providers, of diverse categories, would need to be modified in order to enhance the levels of their learning and skills as relevant to chronic

disease prevention, surveillance, and management. Moreover, currently deployed primary health care providers, of different categories, need to be retrained, along with restructuring of their work schedules, and supported by guidelines to deliver essential chronic care at that level.

The use of trained public health nurses, community health workers, and practitioners of complementary systems of medicine to deliver some of the services currently assigned to physician care providers in primary health care will extend outreach at a lower cost.

Efficient systems for referred care, linking primary care to other levels of provider services (secondary and tertiary) and effective systems for subsequent follow-up care (by primary and secondary care providers) need to be established to ensure cost-effective bidirectional movement of patients across the health care chain.

Empowerment of the community, through effectively communicated health information and support of enabling social environments will allow individuals to perform many tasks related to chronic care in NCDs. This will also help overcome, to some extent, the constraints of limited health care provider resources.

The programme must ensure the availability of essential drugs at affordable prices and meet the technology needs of managing a variety of NCDs.

Estimates of existing and required capacity for NCDs must guide the process of planning. Qualitative and quantitative research methods will help to identify key indicators for such a situational analysis.

As the magnitude of different NCDs varies across social classes, gender and age groups, within the broad framework of integrated chronic care, these varied needs have to be addressed through an appropriate mix of relevant and cost-effective interventions. A mix of public sector provision of free health promotion and health care, social insurance, and private insurance would have to be evolved to enable universal access to NCD interventions.

Concerted efforts must be made to enhance the knowledge of policy-makers and health system managers, at various levels, about the potential impact of cost-effective chronic care interventions and the high costs of 'missed opportunities' so that they become motivated agents for improving the delivery of chronic care.

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