Hypertension Pathologyand its Treatments

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Abstract

Hypertension is also known as high blood pressure. It can produce to severe complications and increase the risk of heart disease,likestroke, and death. Normal blood pressure range is (Systolic) 120/80 (Diastolic) mm of mercury (mmHg), but hypertension occur when higher than 120/80 mmHg. While blood pressure is best regulated through the diet before it reaches the stage of hypertension, there is a range of treatment options Drugs are usually started one at a time at a low dose. Side effects associated with antihypertensive drugs are usually minor diuretics, including thiazides, chlorthalidone, and indapamidebeta-blockers and alpha-blockers calcium-channel blockers angiotensin receptor blockers are most widely used for the treatment of hypertension.

Keywords- Hypertension, Diuretics, angiotensin receptor blockers

INTRODUCTION

Hypertension is defined as Systolic blood pressure (SPB) of ≥140mm Hg and/or diastolic BP (DBP) of ≥ 90 mmHg. Systolic hypertension can occur with DBP ≥90 mm Hg (systolic/diastolic hypertension) or with normal DBP (isolated systolic hypertension), and is the predominant form of hypertension in patients ≥ 60 years old.SBP increases after the age of 50-60years, whereas DBP tends to decrease because of age related changes in arterial vasculature, leading to a widening of pulse pressure (the difference between SBP and DBP). This suggests that SBP is the more important of the two BP components in the aging population. [1]

EPIDEMIOLOGY

Approximately 31% of the population (72 million Americans) has high BP (≥140/90 mm Hg). The percentage of men with high BP is higher than that of women before the age of 45 years, but between the ages of 45 and 54 years the percentage is slightly higher with women. After age 55 years, a much higher percentage of women have high BP than men. Hypertension is more common in younger men compared to younger women. Men have higher blood pressure compared to women up until women reach menopause, at this point, women quickly lose their hormonal protection against hypertension. [2,3]

Prevalence rates are highest in non-Hispanic blacks (33.5%) followed by non-Hispanic whites (28.9%) and Mexican Americans (20.7%). BP values increase with age, and hypertension (persistently elevated BP values) is very common in the elderly. The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is 90%. Most patients have prehypertension before they are diagnosed with hypertension, with most diagnoses occurring between the third and fifth decades of life. In the population age ≥60 years, the prevalence of hypertension in 2000 was estimated at 65.4%, which is significantly higher than the 57.9% prevalence estimated in 1988. [4,5]

CLASSIFICATION OF HYPERTENSION

Hypertension can be classification as either essential (primary or secondary)

1. **Primary or essential hypertension**- Is characterizes by elevation of diastolic BP, a normal cardiac output and an increase in peripheral resistance, about 80 to 90% cases of hypertension belong to primary type of hypertension. Theetiologic of primary hypertension is not clear but several factors are implicated in its genesis. [6] They are;
   - Genetic (family history of vascular disease)
   - Obesity and glucose intolerance
   - High salt intake
   - Cigarette smoking
   - Hyperlipidaemia
   - Increased serum rennin levels
   - Hypersensitivity of sympathetic system
2. **Secondary hypertension**- Is the type where etiology is known. It is Secondary to some disorder, Common disorder causing hypertension are as follows:
   - Acute or chronic renal disease
   - Renal artery stenosis
   - Hyperaldosteronism
   - Cushing's syndrome
   - Acromegaly
   - Pheocromocytoma

CHARACTERISTICS OF HYPERTENSION

There are no characteristics signs or symptoms of hypertension .There is no cure for hypertension ,unless a specific cause is found and corrected .Medical therapy and or lifestyle modification can

control hypertension and in many cases prevent complications .The major consequences of uncontrolled high blood pressure are target organ damage to, Heart, Brain, Kidneys and Eyes .

High blood pressure can only be detected by accurate blood pressure measurement.Individuals with pre- hypertension (those in the range of 130-139/80-89 mmHg) are at twice the risk to develop hypertension as those with lower values. In the U.S., 30% of the population are unaware they have hypertension.[26] The higher the blood pressure,the greater the chance of heart attack, heart failure, stroke and kidney disease, For individuals 40-70 year of age a blood pressure increase 20 mm Hg in systole or 10 mmHg in diastole, doubles the risk of CVD. The Framingham Heart Study showed that individuals who are normotensive (Within normal blood pressure range) at age 55 have a 90% lifetime risk for developing hypertension later in life. Anti- hypertensive therapy has been associated with reductions in stroke incidence averaging 35-40%,heart attack incidence averaging 20-25%, and more than 50% for heart failure. [7]

PATHOPHYSIOLOGY OF PRIMARY HYPERTENSION

Multiple factors modulate the blood pressure (BP) for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. A possible pathogenesis of essential hypertension has been proposed in which multiple factors, including genetic predisposition, excess dietary salt intake, and adrenergic tone, may interact to produce hypertension. Although genetic appears to contribute to essential hypertension, the exact mechanism has not been established. [8, 11]

Due to investigations into the pathophysiology of hypertension, both in animals and humans, growing evidence suggest that hypertension may have an immunological basis. Studies have revealed that hypertension is associated with renal infiltration of immune cells and that pharmacologic immunosuppression (such as occurs with HIV) results in reduced blood pressure in animals and humans .Evidence suggests that T lymphocytes and T- cell derived cytokines (e.g. interleukin 17, tumor necrosis factor alpha) play an important role in hypertension.

One hypothesis is that prehypertension results in oxidation and altered mechanical forces that lead to the formation of neoantigens, which are than presented to T cell , leading to T-cell activation and infiltration of critical organs (e.g. kidney ,vasculature). These results in persistent or severe hypertension and end organ damage.Sympathetic nervous system activation and infiltration and contribute to the pathophysiology of hypertension.[10]

The natural history of essential hypertension evolves from occasional to establish hypertension. After a long invariable asymptomatic period, persistent hypertension develops into complicated hypertension, in which end-organ damages to the aorta and small arteries, heart, kidneys, retina, and central nervous system is evident.[9]

The progression of essential hypertension is as follows:

- Prehypertension in persons aged 10-30 years (by increased cardiac output)
- Early hypertension in person aged 20-40 years (in which increased peripheral resistance in prominent)
- Established hypertension in person aged 30-50 years
- Complicated hypertension in person aged 40-60 years

One mechanism of hypertension has been described as high-output hypertension. High-output hypertension results from decreased peripheral vascular resistance and concomitant cardiac stimulation by adrenergic hyperactivity and altered calcium homeostasis. A second mechanism manifests with normal or reduced cardiac output and elevated systemic vascular resistance due to increased vasoreactivity. Another (and overlapping) mechanism is increased salt and water reabsorption (salt sensitivity) by the kidney, which increases circulating blood volume.[12, 13]

Cortisol reactivity, an index of hypothalamic-pituitary-adrenal function, may be another mechanism by which psychosocial stress is associated with future hypertension.

In a prospective sub study of the Whitehall II cohort, with 3 years follow - up of an occupational cohort in previously healthy patients, investigators reported 15.9% of the patient sample developed hypertension in response to laboratory - induced mental stressors and found an association between cortisol stress reactivity and incident hypertension. [9]

MAJOR RISK FACTORS FOR HYPERTENSION

- **Family history:** The inclusion of heredity as a Contributing factor in the development of Hypertension. It is thought that genetic contribution to HTN is up to 50%. The strength or the prediction depends on the family History & environmental factors.

- **Age related changes in blood pressure:** Maturation & growth are known to cause predictable increases in blood pressure. The arterial blood pressure in the new born is approximately, 50 mmHg systolic & 40 mmHg Diastolic.

- **Race:** Hypertension is more prevalent in blacks than whites. Studies have shown that many black people with hypertension have lower renin level than white people of hypertension.

The suppression of renin has been considered a secondary response to sodium retention & volume excess.

- **Insulin Resistance and Metabolic abnormalities:** Insulin resistance has been found to be more of an acquired trait than a genetic trait. For example, obesity plays an important role in the development of insulin resistance.

- **Excess Alcohol Consumption:** Regular alcohol drinking plays a role in the development of HTN .The recommended safe amount of alcohol is one drink per day for women and two drinks per day for man.

- **High Salt Intake:** Increased salt intake is etiologic factor in the development of hypertension. Salt cause an elevation in blood volume increases the sensitivity of cardiovascular. At present, salt intake among adults united states at least 9 g/day and the far in excess of the maximal intake of 6 g/day adults.

- **Obesity:** Excessive Weight commonly is associated with hypertension the waist to hip ratio commonly is used to differentiate central or upper body obesity. Abdominal or visceral fat seems to cause more insulin resistance, glucose intolerance, dyslipidaemia, hypertension, chronic kidney disease than subcutaneous fat.

- **Dietary intake of potassium, calcium and magnesium:** Low levels of dietary potassium have also been linked to increased blood pressure, various mechanism have been proposed to explain the influence of potassium on blood pressure, including a change in the ratio of sodium to potassium in the diet, a direct natriuretic effect and suppression of renin-angiotensin system.

- **Obstructive sleep Apnoea:** Obstructive Sleep apnoea and hypertension have been Correlated there have various studies that found increased level of norepinephrine, endothelin and aldosterone. [14]

SIGN AND SYMPTOMS

HTN is known as the silent killer because it typically has no warning signs or symptoms, and many people do not know they have it. Even when blood pressure levels are dangerously high, most people do not have any signs or symptoms. A small amount of people may experience symptoms such as dull headaches, vomiting, dizzy spells, and more frequent nosebleeds. These symptoms usually do not occur until blood pressure levels have reached a severe or life-threatening stage. The only way to know for certain if a person has HTN is to have a physician or

other health care professional measures blood pressure, symptoms usually do not occur until blood pressure levels have reached a severe or life-threatening stage. The only way to know for certain if a person has HTN is to have a physician or other health care professional measure blood pressure. There may be certain symptoms to look out for, including. [15,16]

- Severe headache
- Fatigue or confusion
- Vision problems
- Chest pain
- Difficulty breathing
- Irregular heartbeat
- Blood in the urine
- Pounding in your chest, neck, or ears

DIAGNOSIS

Blood pressure is most often measured with a device known as a sphygmomanometer, which Consist of a stethoscope, arm cuff, dial, pump, and valve. Blood pressure is recorded as two Numbers: the systolic and diastolic pressures.

Systolic blood pressure is the maximum pressure during a heartbeat.

Diastolic blood pressure is the lowest pressure between heartbeats.

Blood pressure is measured in millimeters of mercury (mm Hg) and is written systolic over diastolic (for example, 120/80 mm Hg, or 120over80").According to the most recent guidelines, a normal blood pressure is less than 120/80 mmHg. Hypertension is blood pressure that is greater than 140/90. For people over age 60, high blood pressure is defined as 150/90or greater. Prehypertension consist of blood pressure that is 120 to 139/80 to 89.

Blood pressure may increase or decrease, depending on your age, heart condition, emotions, activity, and the medications you take. To make the diagnosis of hypertension, at least three reading that are elevated are usually required.

Medical history (whether have heart problems before)

Assess risk factors (whether smoke, have high cholesterol, diabetes, etc.)

Family history (whether any members of your family have had high blood pressure or heart disease).

Physical exam As part of this exam, he or she may use a stethoscope to listen to your heart for any abnormal sounds and your arteries for a whooshing or swishing sound that may indicate that the artery may be partially blocked. Doctor may also checks the pulses in arm and ankle to determine if they are weak or even absent.

Electrocardiogram (EKG or ECG) a test that measures the electrical activity, rate, and rhythm of your heartbeat via electrodes attached to your arms, legs, and chest. The results are recorded on graph paper.

Echocardiogram this is a test that uses ultrasound waves to provide pictures of the hearts valves and chambers so the pumping action of the heart can be studied and measurement of the chambers and wall thickness of the heart can be made.[18,19]

Laboratory test

Laboratory testing is not diagnostic for hypertension, but tests are frequently ordered to detect conditions that may be causing and /or exacerbating high blood pressure and to evaluate and monitor organ function over time.

General tests that may be ordered include:

- BNP (brain natriuretic peptide) - To detect the change in pressure, cardiac injury and mechanical stretch of heart.
- SGOT (AST) and SGPT (ALT)-To detect any type of liver injury or damage done to the liver due to any type of infection and inflammatory changes.
- Albumin protein, BUN(blood urea nitrogen) and/or creatinine/cystatin-C- To detect and monitor kidney dysfunction or to monitor the effects of medications on the kidneys
- Potassium- As part of the electrolyte panel, which also includes sodium, chloride, and carbon dioxide (CO2); to evaluate and monitor the balance of the body electrolytes. Using syndrome and conn syndrome often cause low potassium, which can be a clue to their presences. Some high blood pressure medications can be a clue to their presence. Some high blood pressure medications can upset the balance by causing excessive loss of potassium or potassium retention.
- Fasting glucose, A1C- To help recognize diabetes and to monitor glucose control over time in diabetic patients.
- Calcium- To determine how much total calcium or ionized calcium is circulating in the blood; increased activity of the parathyroid glands, which produces an increase in serum calcium, is associated with hypertension.

- TSH (thyroid stimulating hormone) and T4- To detect and monitor thyroid dysfunction.
- Lipid profile- To evaluate levels of total cholesterol, HDL cholesterol, LDL, cholesterol and triglycerides and assess the risk of developing atherosclerosis.

The basic metabolic panel (BMP) includes several of the tests listed above, so it may be ordered instead of the individual tests. Specific tests based on the individuals medical history, physical findings, and routine laboratory test results may be ordered to help detect, diagnose, and monitor conditions causing secondary hypertension. They include:

Aldosterone and renin- To help detect the overproduction of aldosterone by the adrenal glands (which may be due to a tumor) or renin by the kidney (which may be due kidney Damage or narrowing of the arteries bringing blood to the kidneys).

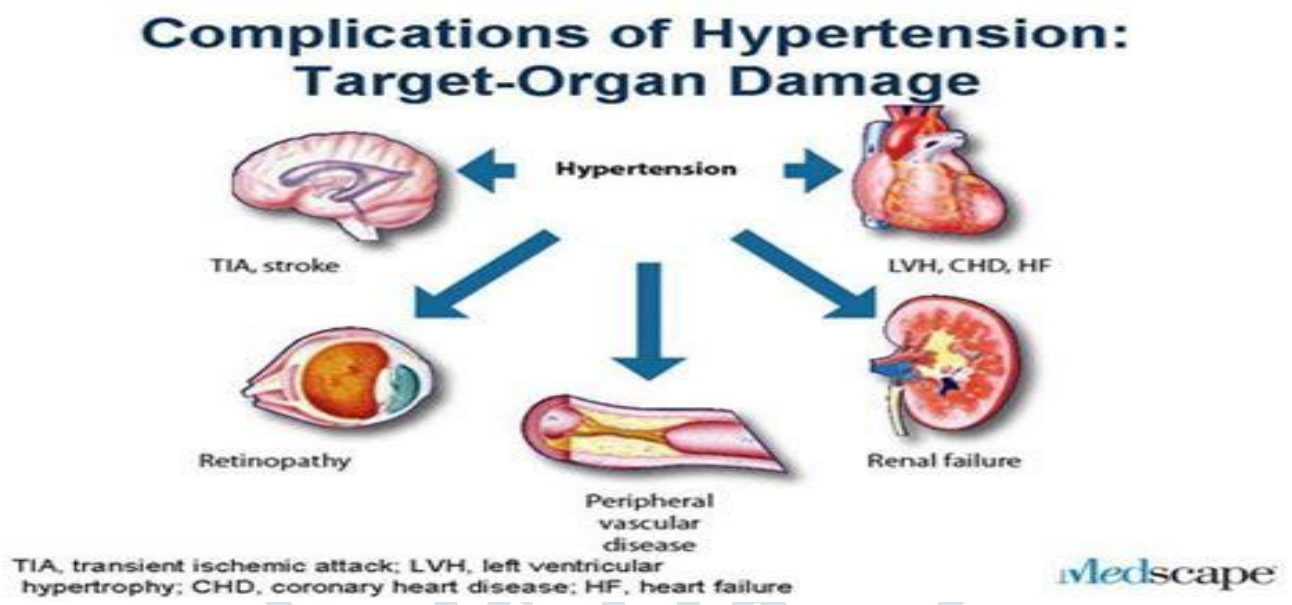
Cortisol- To detect an overproduction of cortisol that may be due to Cushing syndrome.

Catecholamines and metanephries- To measure epinephrine, norepinephrine, and theirMetabolites, primarily to help detect the presence of a pheochrmocytoma that can cause episodes of severe hypertension.[20]

COMPLICATION OF HYPERTENSION

Hypertension mainly Hypertension is a risk factor for all clinical manifestations of atherosclerosis .It is an independent predisposing factor for heart failure , coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD), Myocardial infarction, Stroke, Hypertensive encephalopathy,Dissecting aortic aneurism, Hypertensive nephrosclerosis, Peripheral vascular disease.The major consequences of uncontrolled high blood pressure are target organ damage.

FIG.1 COMPLICATION OF HYPERTENSION



Brain: Hypertension is an important risk factor for brain infarction and haemorrhage. Approximately 85% of strokes are due to infarction and the remainder are due to haemorrhage, either intracerebral haemorrhage or subarachnoid haemorrhage.The incidence of stroke rises progressively with increasing blood pressure particularly systolic blood pressure in individuals >65 years. Treatment of hypertension convincingly decreases the incidence of both ischemic and haemorrhagic stokes .Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50-150mmHg) through a process termed auto regulation of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of auto regulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyper fusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and alterations in mental status.Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours.

Kidney: primary renal disease is the most common etiology of secondary hypertension. Conversely.Hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the entire distribution of blood pressure above optimal.Renal risk appears to more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at level of blood pressure.The atherosclerotic, hypertension-related vascular lesions in the kidney primary affect the preglomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hyper perfusion. Glomenlar pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become

ischemic and gradually atrophic.The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometime extending glomerulus, and may result in focal necrosis of the glomerular tuft.

Heart: Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptation leading to left ventricular hypertrophy, diastolic dysfunction, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and micro vascular disease, and cardiac arrhythmias.Both genetic and hemodynamic factor contribute to left ventricular hypertrophy. Clinically, left ventricular hypertrophy can be diagnosed by electrocardiogram, although echocardiography provides a more sensitive measure of left ventricular wall thickness. Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death.

Peripheral Arteries: 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 increases risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. This is characterized by aching pain in the calves of buttocks while walking that is relieved by rest. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure .An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. Several studies that an ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.[21,22,24]

TREATMENT OF HYPERTENSION

These are two approaches are used for treatment of Hypertension

- Non-pharmacological Treatment
- Pharmacological Treatment

Non-pharmacological Treatment: Non-pharmacological approaches to the reduction of blood pressure generally are advisable as the initial approach to treatment of patient with diastolic blood pressure in the range of 90 to 95 mm Hg. Furthermore, these approaches will augment the effectiveness of pharmacological therapy in patients with higher levels of blood pressure.

To maintain compliance with a therapeutic regimen, the intervention should not lessen the quality of life. All drugs have side effects .If minor alterations of normal activity or diet can reduce blood pressure to a satisfactory level, the complications of drug therapy can be avoided .In addition, non pharmacological method to lower blood pressure allow patients to participate actively in the management of their disease. [25,26,27,28]

Lifestyle Modification:

Educating patients regarding the importance of non-pharmacologic interventions for effective BP control is an important component of reducing cardiovascular risk in the general population. This is particularly true for the pre-hypertensive and hypertensive patient However, aggressive efforts are needed to ensure optimal adherence to these recommendations.

Lifestyle modification include limiting alcohol intake, increasing physical activity, and reducing sodium intake to <6 g of sodium chloride daily. Results from the long-term follow-up of the Trials of Hypertension Prevention (TOHP) study demonstrated that patients who were randomly assigned to a low-salt diet (sodium < 180mg/24 hr.) had a 25% risk reduction in cardiovascular events.

weight reduction of as little as 10 to 12 pounds in an obese hypertensive patient can have a considerable effect on elevated BP. Appropriate nutritional counselling can encourage a diet with reduced total fat and cholesterol intake, in addition to providing an adequate daily intake of potassium,calcium, and magnesium. The Dietary Approaches to stop Hypertension (DASH) trial has provided substantial data that a diet rich in fruits, nuts, vegetables, and low-fat dairy products and with an emphasis on fish and chicken rather than red meat lowered BP even without weight reduction and was particularly effective in those who also restricted sodium chloride intake.

Dietary recommendations must be made on an individualized basis and should be well supported with continued educational and counselling efforts. Cigarette smoking is a recognized accelerator of cardiovascular disease. Smoking cessation should therefore be strongly encouraged for all patients, and education, counselling and medication should be provided as needed.[29,30]

TABLE. 1 FOR LIFESTYLE MODIFICATION TO MANAGE HYPERTENSION

Lifestyle modification to manage hypertension.		
Modification	Recommendation	Average systolic blood pressure reduction range.
Weight Reduction	Maintain normal body weight (BMI 18.5-24.9 kg/m)	5-20 mmHg/10 kg weight loss
DASH eating plan	Consume a diet rich in fruits vegetables, and low-fat dairy products with a reduced content of saturated and total fat.	8-14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to more than 100mmol per day (2.4 g sodium of 6 g sodium chloride)	2-8 mmHg
Physical activity	Engage in regular aerobic physical activity such as brick walking (at least 30 min/day most day of the week)	4-9 mmHg
Moderation of alcohol consumption	Limit consumption to on more than 2 drinks (24OZ beer, 10 OZ wine, or 3OZ 30 proof Whiskey)/day in most men and no more than 1 drink/day in women.	2-4 mmHg

DASH, Dietary Approaches to Stop Hypertension.

- For overall cardiovascular risk reduction, stop smoking.
- The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

Pharmacological Treatment: These are excellent clinical outcome trial data proving that lowering BP with several classes of drugs, including angiotensin converting enzyme inhibitors (ACEIs) ,angiotensin receptor blockers (ARBs),beta - blockers (BBs),calcium channel blockers (CCBs),and thiazide -type diuretic,will all reduce the complications of hypertension .Thiazides - types diuretics have been the basis of antihypertensive therapy in most outcome trials.In these trials, including the recently published Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT) diuretics have been virtually unsurpassed in preventing the cardiovascular complication of Hypertension.[31]

TABLE.2 Drug Treatment

CLASS	DRUGS
ACE inhibitor	Ramipril, Captopril, Enalapril.
Angiotensin (ATI) receptor Antagonists	Losartan,Telmisartan, valsartan Candesartan.
Calcium channel blockers	Amlodipine, Nifedipine, Felodipine, Verapamil, Diltiazem.
Diuretics	Thiazide:- Hydrochlorothiazide, chlorthalidone Loop Diuretics:- furosemide, bumetanide Potassium sparing:- spironolactone, amiloride
Beta blockers	Propranolol, Atenolol,Metoprolol
Alpha blockers	Prazosin,Doxazocin
Vasodilators	Hydralazine,Minoxidil,Sodium Nitroprusside

Diuretics enhance the antihypertensive efficacy of multidrug regimens, can be useful in achieving BP control, and are more affordable than other antihypertensive agents. Despite this finding remains underutilized. Thiazide-type diuretic should be used as initial therapy for most patients with hypertension , either alone or in combination with one of the other classes (ACEIs , ARBs, BBs, CCBs) demonstrated to be beneficial in randomized controlled outcome trials.

ACE Inhibitors: Ramipril

Mechanism of Action: Inhibits ACE, perverting conversion of angiotensin I to angiotensin II, leading to: reduced peripheral arterial resistance, aldosterone secretion and accumulation of bradykinin. Angiotensin-converting enzymes (ACE) inhibitor help relax blood vessels. ACE inhibitors prevent an enzyme in your cardiovascular system by narrowing your blood vessels and releasing hormones that can raise your heart to work harder.[32]

Adverse effects: Hypotension**,** Persistent angioedema, Rash, Dry cough.

Angiotensin Receptor Blockers

ARBs antagonise the action of angiotensin II in a highly selective manner at the angiotensin II ATI- receptor. Angiotensin II receptors are sub classified into ATI and AT2 receptor.The ATI-receptor mediates all the classical effects of angiotensin II e.g. vasoconstriction, aldosterone release, sympathetic activation and other potentially harmful effects on the cardiovascular system. The functional role of the AT2- receptor is unclear. Because many tissues contain enzymes pathways capable of converting angiotensin I to angiotensin II independent of angiotensin converting enzyme (ACE), there are theoretical advantages in blocking the rennin -angiotensin system via the ATI-receptor compared with ACE inhibition.Many ARBs or active metabolites bind to the ATI-receptor in a manner which is competitive but slowly surmountable, so that duration of action is a prolonged. Reduction in blood pressure secondary to vasodilation following angiotensin receptor blockade is greatest when the rennin-angiotensin system is activated (e.g. following diuretic therapy or renal artery stenosis) but ARBs also lower blood pressure when there is normal or low activity of the rennin-angiotensin system. ARBs do not produce cough as it is major adverse effect with ACE inhibitors.[33,34]

Losartan

Mechanism of action: Losartan is selective, competitive Angiotensin II receptors type I (ATI) receptor antagonist, reducing the end organ responses to angiotensin II. Losartan administration result in a decrease in total peripheral resistance (after load) and cardiac venous return (preload) All of the physiological effects of angiotensin II, including stimulation of release of aldosterone, antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the rennin-angiotensin system.

Adverse effects: Hypertension, Hyperkalaemia, Headache, Dizziness, Weakness, Diarrhoeas.

Diuretics

Diuretics increase urinary excretion of water and electrolytes and are used to relieve edema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral oedema, and also to lower raised intraocular pressure. Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; Diuretics increase urinary excretion of water and electrolytes and are used to relieve edema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect. [30]

Thiazide diuretics: hydrochlorothiazide

Mechanism of Action

Hydrochlorothiazide act by inhibiting sodium and chloride reabsorption at the beginning of the distal convoluted tubule, it is used in the management of edema associated with mild to moderate congestive heart failure, renal dysfunction or hepatic disease.

Adverse effects: hypokalemia, hypomagnesaemia, hypernatremia, hypochloraemic alkalosis hypocalcaemia, hyperglycemia, hyperuricaemia, gout, rash, photosensitivity; altered plasma lipid concentration, rarely impotence pancreatitis, intrahepatic cholestasis and hypersensitivity reactions (including pneumonitis, pulmonary edema, severe skin reactions) also reported, acute renal failure Loop doses of diuretics used to treat hypertension.[33,35]

Calcium Channel Blocker: Amlodipine

Mechanism of Action:

Amlodipine selectively inhibits the Trans membrane influx of calcium ions into the vascular smooth and cardiac muscle. A decrease in intracellular calcium inhibits the contractility of the myocardial smooth muscle cells. This results in the dilation of coronary and systemic arteries with a greater pharmacological effect on the vascular smooth muscles than the cardiac muscle. The ultimate effect of amlodipine is a reduction in peripheral vascular resistance and reduction in blood pressure. Amlodipine does not significantly affect sinus node function, cardiac conduction, or have negative inotropic effects at clinical dosed.The gradual pharmacological effect of

amlodipine does not produce tachycardia caused by other peripheral vasodilators. Serum calcium levels are unaffected by amlodipine. [31]

Adverse effects: Palpitation, Flushing, Headache, Dizziness, Peripheral oedema, Nausea, Drowsiness, Muscle cramps.

PREVENTION OF HYPERTENSION

The low prevention of hypertension in some communities indicates that hypertension is potentially preventable.The WHO has recommended the following approaches in the prevention of hypertension:

1. Primary prevention
    (a) Population strategy
    (b) High-risk strategy
2. Secondary prevention

1.PRIMARY PREVENTION

Although control of hypertension can be successfully achieved by medication (secondary prevention) the ultimate goal in general is primary prevention. Primary prevention has been defined as "all measures to reduce the incidence of disease in a population by reducing the risk of onset ". The earlier the prevention starts the more likely it is to be effective .

In connection with primary prevention, terms such as "population strategy "and "high -risk strategy "have become established.The WHO has recommended these approaches in the prevention of hypertension. Both the approaches are complementary.

a. POPULATION STRATEGY

The population approach is directed at the whole population , irrespective of individual risk levels. The concept of population approach is based on the fact that even a small reduction in the average blood pressure of a population would produce a large reduction in the incidence of cardiovascular complication such as stroke and CHD.The goal of the population approach is to shift the community distribution of blood pressure towards lower levels of "biological normality.[2] This involves a multifactorial approach, based on the following non-pharmacotherapeutic intervention:

(a) NUTRITION : Dietary changes are of paramount importance. These comprise :

(i) Reduction of salt intake to an average of not more than 5 g per day.(ii) Moderate fat intake. (iii) The avoidance of a high alcohol intake , and (iv) restriction of energy intake appropriate to body needs.

(b) WEIGHT REDUCTION: The prevention and correction of overweight/obesity (Body mass index greater than 25) is a prudent way of reducing the risk of hypertension and indirectly CHD, it goes with dietary changes.

(c) EXERCISE PROMOTION: The evidence that regular physical activity leads to a fall in body weight, blood lipids and blood pressure goes to suggest that regular physical activity should be encouraged as part of the strategy for risk -factor control.

(d) BEHAVIOURAL CHANGES : Reduction of stress and smoking , modification of personal life-style ,yoga and transcendental meditation could be profitable.

(e) HEALTH EDUCATION: The general public require preventive advice on all risk factors and related health behaviour. The whole community must be mobilized and made aware of the possibility of primary prevention, and

(f) SELF-CARE: An important element in community - based health programmes is patient participation .The patient is taught self-care, i.e. ,to take his own blood pressure and keep a log-book of his readings .By doing so, the burden on the official health services would be considerably reduced. Log-book can also be useful for statistical purposes and for the long -term follow-up of cases.

b. HIGH-RISK STRATEGY :

This is also part of primary prevention. The aim of this approach is "to prevent the attainment of levels of blood pressure at which the institution of treatment would be considered". This approach is appropriate if the risk factors occur with very low prevalence in the community Detection of high -risk subjects should be encouraged by the optimum use of clinical methods. Since hypertension tends to cluster in families, the family history of hypertension and "tracking" of blood pressure from childhood may be used to identify individuals at risk.

2. SECONDARY PREVENTION:

The goal of secondary prevention is to detect and control high blood pressure in affected individuals. Modern antihypertensive drug therapy can effectively reduce high blood pressure and consequently,the excess risk of morbidity and mortality from coronary, cerebrovascular and kidney disease. The control measures comprise:

(i) EARLY CASE DETECTION : Early detection is a major problem. This is because high blood pressure rarely causes symptoms until organic damage has already occurred, and our aim should be to control it before this happens.The only effective method of diagnosis of hypertension is to screen the population. But screening,that is not linked to follow-up and sustained care. It is emphasized that screening should not be initiated if health resources for treatment and follow-up are not adequate.

In the developed countries, mass screening is not considered essential for the adequate control of blood pressure in the population.In Europe, the large majority of people have at least one contact in every 2 years with the health service.If blood pressure is measured at each such contact, the bulk of the problem of detecting those in need in intervention is solved.

(ii) TREATMENT: In essential hypertension, as in diabetes, we cannot treat the cause, because we do not know what it is.Instead, we try to scale down the high blood pressure to acceptable levels. The aim of treatment should be to obtain a blood pressure below 140/90, and ideally a blood pressure of 120/80. Control of hypertension has been shown to reduce the incidence of stroke and other complications. This is a major reason for identifying and treating asymptomatic hypertension. Care of hypertensive should also involve attention to other risk factor such as smoking and elevated blood cholesterol levels.

(iii) PATIENT COMPLIANCE: The treatment of high blood pressure must normally be life-long and this presents problems of patient compliance, which is defined as "the extent to which patient behaviour (in terms of taking medicines, following diets or executing other lifestyle changes) coincides with clinical prescription". The compliance rates can be improved through education directed to patients, families and the community.

Intensive research carried out during the past decade, aiming at control of hypertension at the community levels ,has already provided valuable results. The studies have shown that control of hypertension in a population is feasible,that it can be carried out through the existing system of health services in different countries, and that the control of blood pressure leads to a reduction of complication of high blood pressure - namely stroke, heart failure and renal failure. In some of the

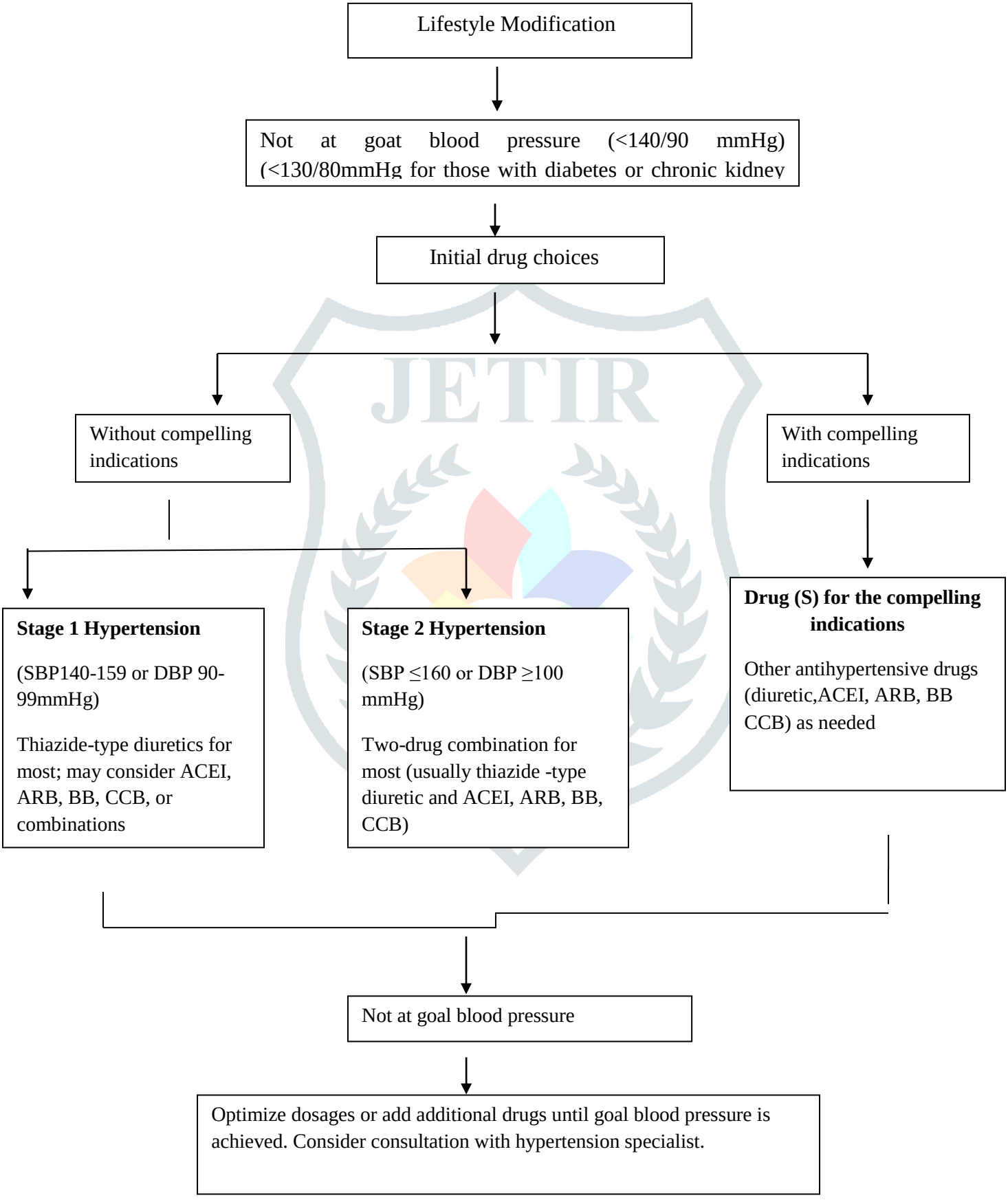
projects the incidence of myocardial infarction was also reduced. As a result of these findings some countries have launched nationwide control programmes in the field of hypertension. [25,41]

MANAGEMENT

JOINT NATIONAL COMMITTEE VII

In 2003 the National High Blood Pressure Education Program presented the complete seventh Report of the joint National Committed on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Like its predecessors, the purpose is to provide an evidence-based approach to the prevention and management of hypertension. The key messages of this report are these: in those older than age 50, systolic blood pressure (BP) of greater than 140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP; beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg; those who are normotensive at 55 year of age will have a 90% lifetime risk of developing hypertension; pre-hypertensive individuals (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)require health-promoting lifestyle modification prevent the progressive rise in blood pressure and CVD, for uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes; this report delineates specific high-risk conditions that are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers), two or more antihypertensive medications will be required to achieve goal BP (140/90 mmHg or 130/80 mmHg) for patients with diabetes and chronic kidney disease, for patients whose BP is more than 20 mmHg above the systolic BP goal or more than 10 mmHg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered, regardless of therapy or care, hypertension will be controlled only if patient are motivated to stay on their treatment plan. Positive experiences trust in the clinician and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgment remains paramount. [23,36,37]

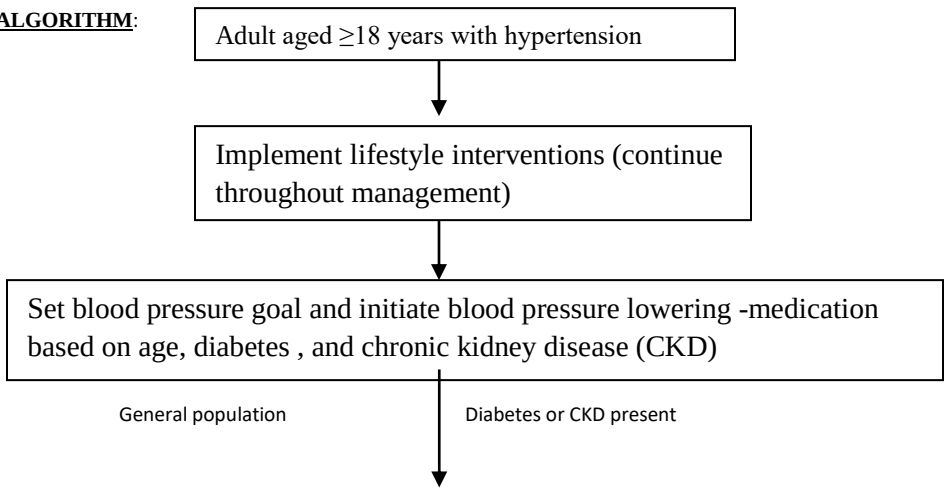
JNC 7HYPERTENSION GUIDELINES ALGORITHMS

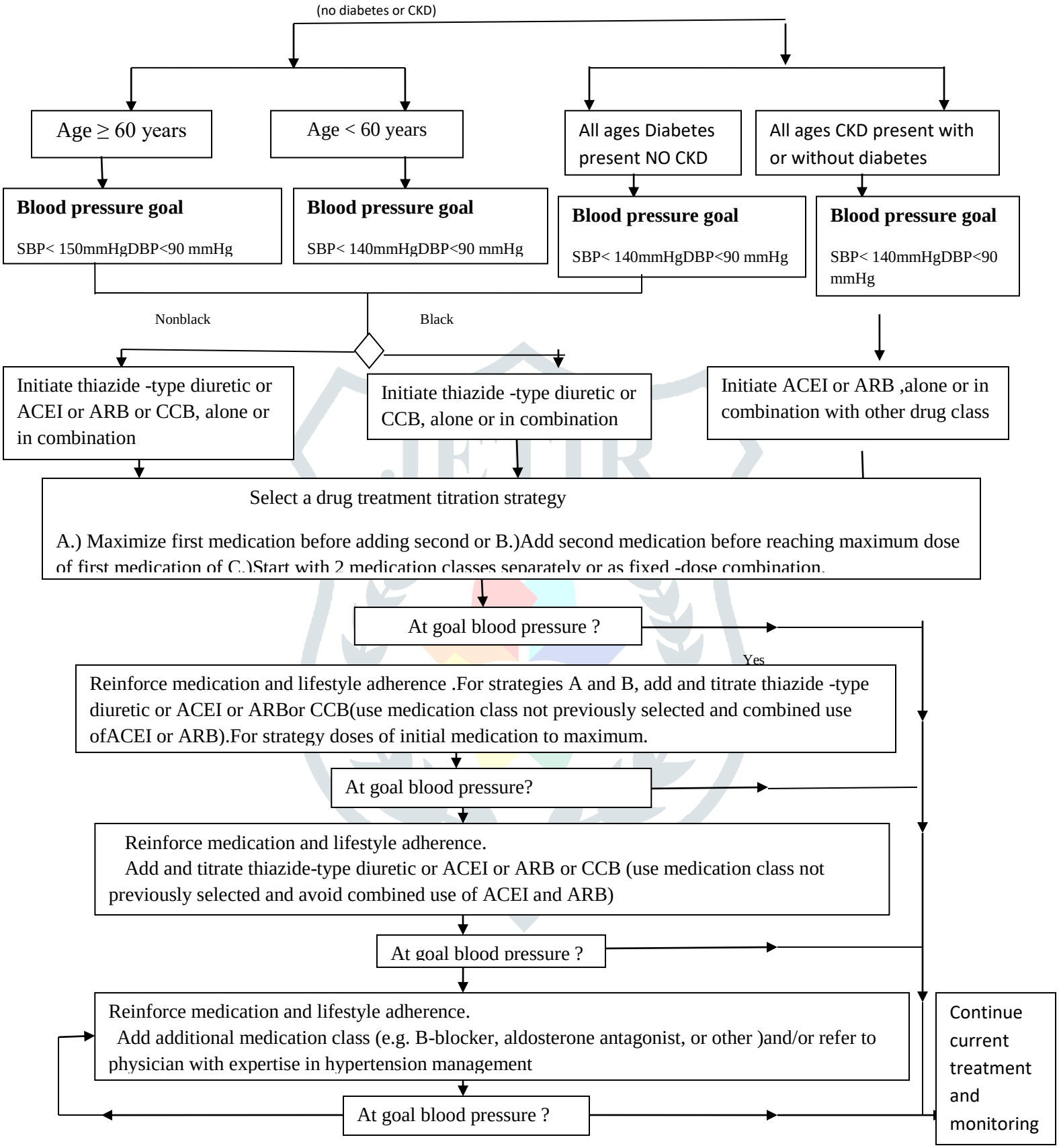


JOINT NATIONAL COMMITTEE VIII

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension evidence- based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trial s, which represent the gold standard for determining efficacy and effectiveness .Evidence quality and recommendation were graded based on their effect on important outcomes. There is strong evidence to support treating hypertensive persons aged 60 year or older to a BP goal of less than 150/90 mmHg and hypertensive persons 30 through 59 year of age to a diastolic goal of less than 90 mmHg; however, there is insufficient evidence in hypertensive person younger than 60 years for a systolic goal, or in those younger than 30 years for diastolic goal, so the panel recommends a BP of less than 140/90 mmHg for those groups based on expert opinion.[50] The same thresholds and goal are recorded for hypertensive adults with diabetes of non-diabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic the nonblack hypertensive population, including those with diabetes, a calcium channel blocker or thiazide -type diuretic is recommended as initial therapy .Therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blockers in person with CKD to improve kidney outcome. Although this guideline provides evidence based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendation are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. [38,39,40

JNC 8 GUIDELINES ALGORITHM:




(no diabetes or CKD)
Age ≥ 60 years
Age < 60 years
All ages Diabetes present NO CKD
All ages CKD present with or without diabetes
Blood pressure goal
SBP< 150mmHgDBP<90 mmHg
Blood pressure goal
SBP< 140mmHgDBP<90 mmHg
Blood pressure goal
SBP< 140mmHgDBP<90 mmHg
Blood pressure goal
SBP< 140mmHgDBP<90 mmHg
Nonblack
Black
Initiate thiazide -type diuretic or ACEI or ARB or CCB, alone or in combination
Initiate thiazide -type diuretic or CCB, alone or in combination
Initiate ACEI or ARB ,alone or in combination with other drug class
Select a drug treatment titration strategy
A.) Maximize first medication before adding second or B.)Add second medication before reaching maximum dose of first medication of C.)Start with 2 medication classes separately or as fixed -dose combination.
At goal blood pressure ?
Yes
Reinforce medication and lifestyle adherence .For strategies A and B, add and titrate thiazide -type diuretic or ACEI or ARBor CCB(use medication class not previously selected and combined use ofACEI or ARB).For strategy doses of initial medication to maximum.
At goal blood pressure?
Reinforce medication and lifestyle adherence.
Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB)
At goal blood pressure ?
Reinforce medication and lifestyle adherence.
Add additional medication class (e.g. B-blocker, aldosterone antagonist, or other)and/or refer to physician with expertise in hypertension management
At goal blood pressure ?
Continue current treatment and monitoring

URIC ACID

Uric acid is the end product of the degradation of purines. Because uric acid serves no known physiologic purpose, it is regarded as a waste product. Normal uric acid levels are near the limits of urate solubility, because of the delicate balance that exists between the amount of urate produced and excreted. Humans have higher uric acid levels than other mammals because they do not express the enzyme uricase, which converts uric acid to the more soluble allantoin**.**

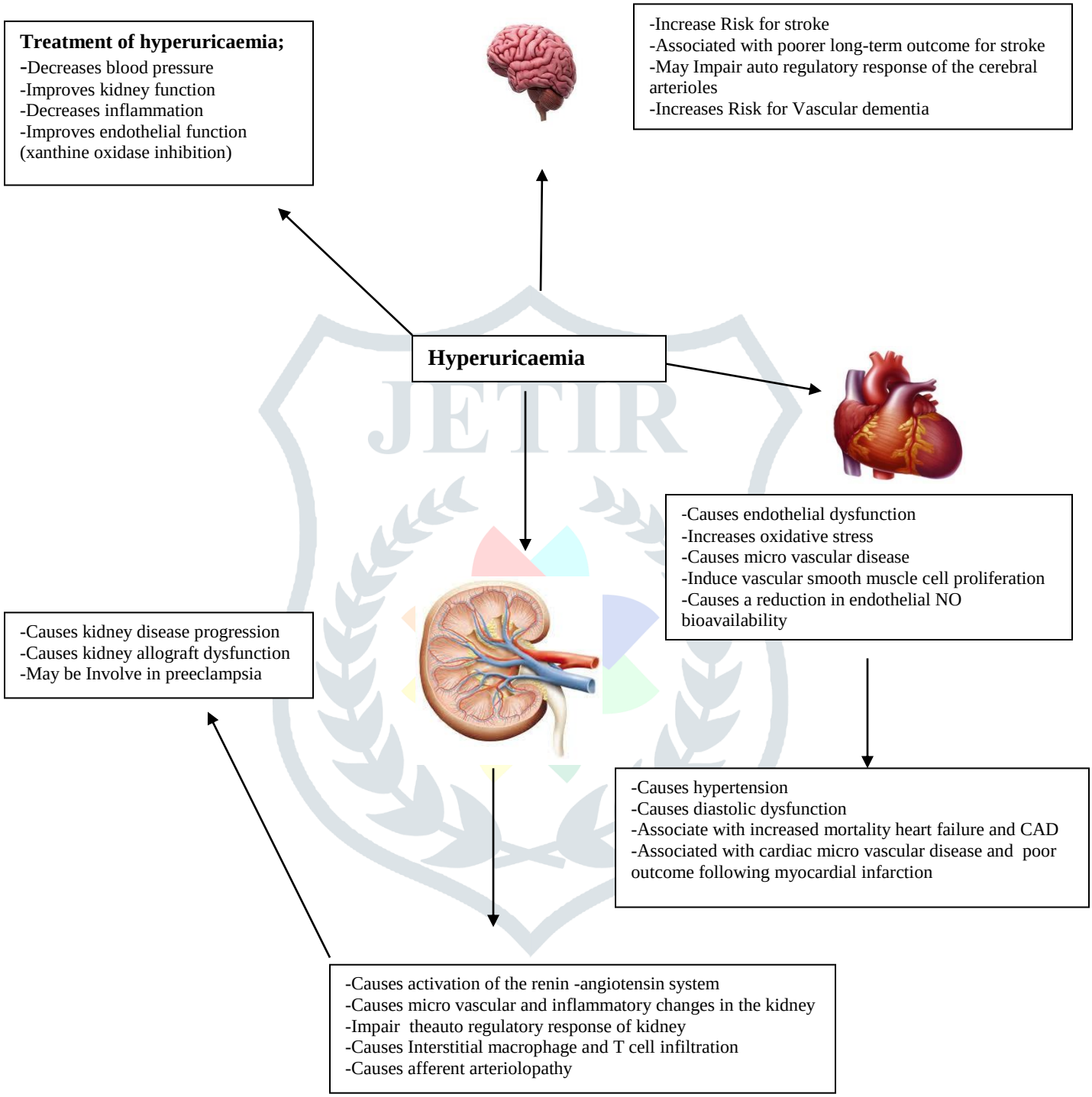
PHYSIOLOGY

Uric acid is the end product of the degradation of purines. It serves no known physiologic purpose and is regarded as a waste product. [68] The size of the urate pool is increased several fold in individuals with gout. This excess accumulation may result from either overproduction or under excretion.[69]

The purines from which uric acid is produced originate from three sources: dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.Abnormalities in the enzyme systems that regulate purine metabolism may result in overproduction of uric acid. An increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase leads to an increased concentration of PRPP, a key determinant of purine synthesis and thus uric acid production.[70] A deficiency of hypoxanthine–guanine phosphoribosyl transferase may also result in overproduction of uric acid. HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid. These two conversions require PRPP as the substrate and are important reutilization reactions involved in nucleic acid synthesis. A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid and more PRPP to interact with glutamine in the first step of the purine pathway.[71,72,73] Complete absence of HGPRT results in the childhood Lesch-Nyhan syndrome, characterized by choreoathetosis, spasticity, mental retardation, and markedly excessive production of uric acid.

Uric acid may also be overproduced as a consequence of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymph proliferative disorders. Cytotoxic drugs used to treat these disorders can also result in overproduction of uric acid due to lysis and breakdown of cellular matter.[41]

FIG.2 RELATION BETWEEN HYPERTENSION AND URIC ACID



Uric acid is a weak acid, and the majority of uric acid (about 98%) circulates in the blood as ionisedurate. Because of the high concentration of sodium in the extracellular compartment, urate is largely present as monosodium urate with a low solubility. The consumption of foods rich in purines and protein, obesity, alcohol, and soft drinks sweetened with fructose could make serum uric acid level a dramatic increase. In addition, elevated uric acid may also be closely associated

with low-level lead intoxication, which causes a decline in renal function. High uric acid levels have been traditionally considered a risk factor for gout and hyperuricaemia. However, it has emerged recently that high serum uric acid level is a risk factor of cardiovascular disease. It is suggested that the relation between uric acid and cardiovascular disease (CVD) is evident not only in the presence of overt hyperuricaemia but also with serum uric acid levels considered in the normal to high range (>5.2 to 5.5 mg/dL).[42]

- Uric acid is the final product of purine metabolism in humans and higher primates, and has been postulated to play a role in antioxidation. A number of recent studies have shown that higher serum uric acid levels associate with surrogate markers of better bone health, leading to speculation about a potential protective role of uric acid against bone loss.One proposed mechanism by which hyperuricaemia could contribute to higher BMD is via the potential anti-oxidant effects of uric acid, which in turn may inhibit osteoclastic bone resorption.
- Another recent observational study in peri- and postmenopausal women showed a similar positive correlation between serum uric acid and bone mineral density and in the rate of change in bone mineral density over time.[43]
- Dietary purines play an unimportant role in the generation of hyperuricaemia in the absence of some derangement in purine metabolism or elimination.
- About two-thirds of the uric acid produced each day is excreted in the urine. The remainder is eliminated through the GI tract after enzymatic degradation by colonic bacteria. A decline in the urinary excretion of uric acid to a level below the rate of production leads to hyperuricaemia and an increased miscible pool of sodium urate.
- Drugs that decrease renal clearance of uric acid through modification of filtered load or one of the tubular transport processes include diuretics, nicotinic acid, salicylates (less than 2 g/day), ethanol, pyrazinamide, levodopa, cyclosporine, and cytotoxic drugs.
- The average human produces 600 to 800 mg of uric acid daily and excretes less than 600 mg in urine. Individuals who excrete more than 600 mg after being on a purine-free diet for 3 to 5 days are considered overproducers. Hyperuricaemia individuals who excrete less than 600 mg of uric acid per 24 hours on a purine-free diet are defined as underexcretorsofuric acid. On a regular diet, excretion of more than 1,000 mg per 24 hours reflects overproduction, less than this is probably normal.
- Deposition of urate crystals in synovial fluid results in an inflammatory process involving chemical mediators that causes vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorph nuclear leukocytes. Phagocytosis of

urate crystals by leukocytes results in rapid lysis of cells and a discharge of proteolytic enzymes into the cytoplasm. The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth, and swelling.

- Uric acid nephrolithiasis occurs in 10% to 25% of patients with gout. Predisposing factors include excessive urinary excretion of uric acid, acidic urine, and highly concentrated urine.
- In acute uric acid nephropathy, acute renal failure occurs as a result of blockage of urine flow secondary to massive precipitation of uric acid crystals in the collecting ducts and ureters. This syndrome is a well-recognized complication in patients with myeloproliferative or lymph proliferative disorders and results from massive malignant cell turnover, particularly after initiation of chemotherapy. Chronic urate nephropathy is caused by the long-term deposition of urate crystals in the renal parenchyma.[43,44,45]

OSTEOPOROSIS

Bone is the substance that forms the skeleton of the body. it is composed chiefly of calcium phosphate and calcium carbonate. The bones have two components – the cortical bone which is dense, solid, and surrounds the marrow space and the trabecular bone which is composed of a honeycomb-like network of trabecular plates and rods interspersed in the bone marrow compartment.[46]

The periosteum is a fibrous connective tissue sheath that surrounds the outer cortical surface of bone, except at joints where bone is lined by articular cartilage. It contains blood vessels, nerve fibers, osteoblasts, and osteoclasts. It protects, nourishes, and aides in bone formation. . It plays an important role in appositional growth and fracture repair. The endosteum is a membranous structure covering the inner surface of cortical and cancellous bone and the blood vessel canals (Volkmann's canals) present in bone.[47]

Physiology of Bone Formation:

Bone is composed of support cells, namely, osteoblasts and osteocytes, remodeling cells, namely, osteoclasts; and non-mineral matrix of collagen and non-collagenous proteins called osteoid , with inorganic mineral salts deposited within the matrix. During life, the bones undergo processes of longitudinal and radial growth, modeling (reshaping), and remodeling.[47,48]

A. **Bone Formation**Ossification (or osteogenesis) is the process of formation of new bone by cells called osteoblasts. These cells and the bone matrix are the two most crucial elements

involved in the formation of bone. This process of formation of normal healthy bone is carried out by two important processes, namely:

1. Intramembranous ossification characterized by laying down of bone into the primitive connective tissue (mesenchyme) resulting in the formation of bones (skull, clavicle, mandible). It is also seen in the healing process of fractures (compound fractures) treated by open reduction and stabilization by metal plate and screws. [49]
2. Endochondral ossification where a cartilage model acts as a precursor (e.g., femur, tibia, humerus, radius). This is the most important process occurring during fracture healing when treated by cast immobilization. If the process of formation of bone tissue occurs at an extra skeletal location, it is termed as heterotopic ossification.

Three basic steps involved in osteogenesis are:

(a) Synthesis of extracellular organic matrix (osteoid)

(b) Matrix mineralization leading to the formation of bone

(c) Remodeling of bone by the process of resorption and reformation

Osteoblasts

Osteoblasts originate from mesenchymal stem cells of the bone marrow stroma and are responsible for bone matrix synthesis and its subsequent mineralization.

Osteoblasts are mononucleated, and their shape varies from flat to plump, reflecting their level of cellular activity, and, in later stages of maturity, lines up along bone-forming surfaces.

Osteoblasts are responsible for regulation of osteoclasts and deposition of bone matrix. Osteocytes are the most abundant cells in bone, these cells communicate with each other and with the surrounding medium through extensions of their plasma membrane. The osteoblasts, rich in alkaline phosphatase, an organic phosphate-splitting enzyme, possess receptors for parathyroid hormone and estrogen. Also, hormones, growth factors, physical activity, and other stimuli act mainly through osteoblasts to bring about their effects on bone. [50]

Bone Matrix

The structure of bone is constituted by:

(A) Inorganic (69 %) component, consisting of hydroxyapatite (99 %)

(B) Organic (22 %), constituted by collagen (90 %) and noncollagen structural proteins which include proteoglycans, sialoproteins, glacontaining proteins, and 2HS-glycoprotein

Osteocytes

Osteocytes represent terminally differentiated osteoblasts and function within syncytial networks to support bone structure and metabolism. Osteocytes are linked metabolically and electrically through gap junctions composed primarily of connexin. Osteocyte apoptosis in response to estrogen deficiency or glucocorticoid treatment is harmful to bone structure.

Bone Minerals

Crystalline hydroxyapatite [Ca10 (PO 4)6(OH) 2] is the chief mineral component of bone, constituting approximately about a quarter of the volume and half of the mass of normal adult bone. The end result is a highly organized amalgam of protein, primarily collagen, and mineral, primarily hydroxyapatite, that has sufficient structural integrity to serve the mechanical functions of the skeleton.

Ossification

Ossification mainly occurs during formation of the flat bones of the skull but also the mandible, maxilla, and clavicles.

The steps in intramembranous ossification

1. Formation of ossification center
2. Calcification
3. Formation of trabeculae
4. Development of periosteum

Primary Center of Ossification

Formation of Periosteum: Once vascularized, the perichondrium becomes the periosteum.

Formation of Bone Collar: The osteoblasts secrete osteoid against the shaft of the cartilage model (appositional growth). This serves as support for the new bone.

Calcification of Matrix: Chondrocytes in the primary center of ossification begin to grow.

Invasion of Periosteal Bud: The hypertrophic chondrocytes (before apoptosis) secrete vascular endothelial cell growth factor that induces the sprouting of blood vessels from the perichondrium.

Secondary Center of Ossification

A secondary ossification center appears in each end (epiphysis) of long bones. The cartilage between the primary and secondary ossification centers is called the epiphyseal plate, and it continues to form new cartilage, which is replaced by bone, a process that results in an increase in length of the bone.

B. Bone Modeling

Modeling (reshaping) is the process by which bones change their overall shape in response to physiologic influences or mechanical forces, leading to gradual adjustment of the skeleton to the forces that it encounters. Bones may widen or change axis by removal or addition of bone to the appropriate surfaces by independent action of osteoblasts and osteoclasts in response to biomechanical forces.[51,52,53,54]

C. Bone Remodeling

Bone remodeling is a lifelong process wherein old bone is removed from the skeleton and new bone is added. Remodeling involves continuous removal of discrete packets of old bone, replacement of these packets with newly synthesized proteinaceous matrix, and subsequent mineralization of the matrix to form new bone. [54, 55, 56]

Bone disorders

Osteoporosis is a very common metabolic disorder of the skeleton, where in the bone mineral density (BMD) is reduced, the bone microarchitecture is disrupted (perforation of trabecular plates), and the amount and variety of non-collagenous proteins in bone is altered, leading to increased risk of fracture. Osteoporosis may be: Primary (postmenopausal/senile) Secondary cause (nutrition, endocrine, drug, malignancy, chronic disease, idiopathic).

The loss of bone mass and strength can be contributed by: (a) Failure to reach an optimal peak bone mass as a young adult (b) Excessive resorption of bone after peak mass has been achieved (c) An impaired bone formation response during remodeling[57,58]

Paget's disease

In this disorder, the osteoclasts become abnormally activated, possibly by viral infection, and produce a bizarre and irregular pattern of resorption, to which there is usually an intense osteoblastic response with irregular new bone formation often in the form of woven bone. Thus, in Paget's disease there may be increased bone density, but because of the irregular architecture, bone strength is decreased and pathologic fractures may occur.

Osteomalacia/Rickets

The growth plates affecting children is seen in rickets, while in osteomalacia affecting adults, there is incomplete mineralization of osteoid. There is decrease in Ca/PO_4 ratio, increase in alkaline phosphatase, and decrease in calcium excretion [$Ca \times PO_4 < 2.4$].

Osteopetrosis

Osteopetrosis or osteosclerosis in which bone resorption is defective because of impaired formation of osteoclasts or loss of osteoclast function. In these disorders, bone modeling as well as remodeling is impaired, and the architecture of the skeleton can be quite abnormal.[59]

OBESITY

Obesity is a physical state resulting from energy imbalance, where the number of calories consumed is greater than that expended by physical activity. Obesity is characterized by excess body fat and associated with an increased risk of cardiovascular disease, hypertension, type 2 diabetes mellitus (T2DM), some cancers, liver and gall bladder disease, musculoskeletal conditions, fibromyalgia, unilateral plantar fasciitis and gout. [34] Metabolic syndrome describes an amalgamation of metabolic abnormalities, typically characterized by abdominal obesity, insulin resistance, hyperglycemia, hypertension, dyslipidemia and hypertriglyceridemia. [46]

Social and economic development and urbanization have increased access to and dependence on high fat, energy rich, convenient foods. This has contributed to a nutritional transition, with increased consumption of high fat, high sodium, and energy dense foods and away from traditional high fiber, high protein diets. [47]

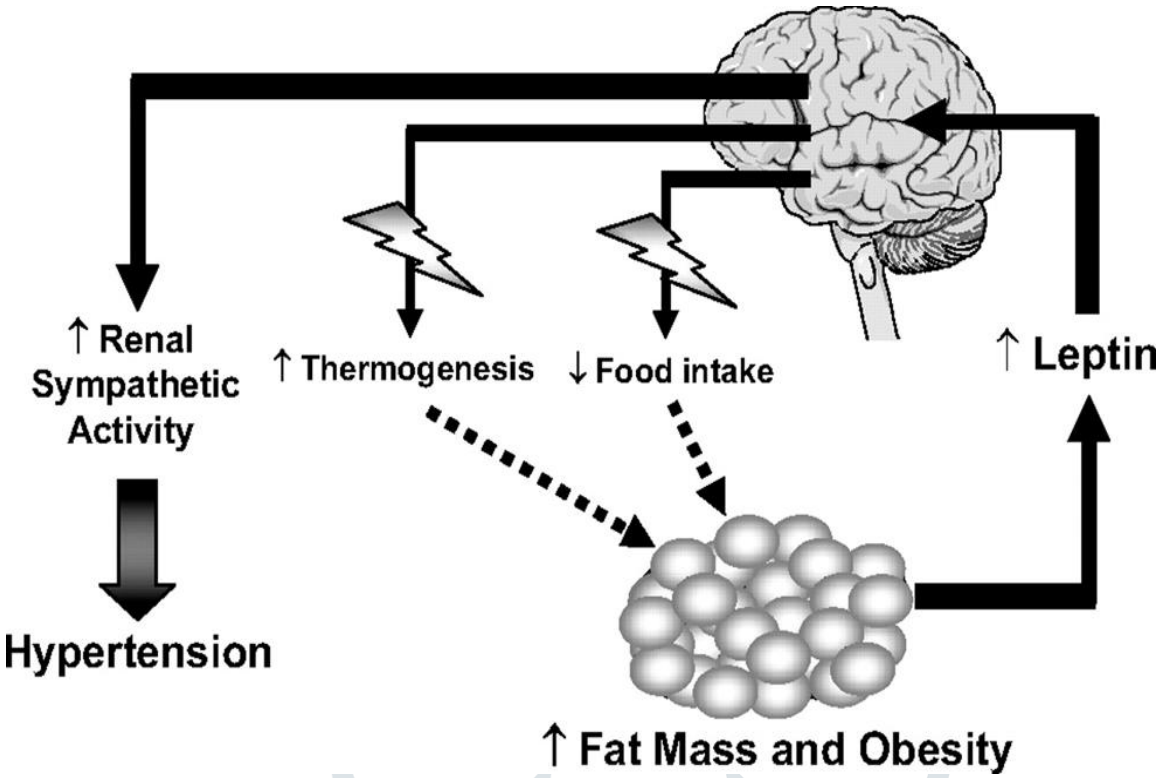
The World Health Organization (WHO) defined overweight as a BMI of 25 to 29.9 kg/m2 and obesity as a BMI greater than or equal to 30 kg/m^2. Global prevalence of obesity has rapidly increased and continues to increase. The WHO estimates that around 1.2 billion people worldwide are overweight with at least 300 million of these individuals being obese. In India, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.[48,57]

Progression from a normotensive to hypertensive phenotype results from a combination of genetic, environmental, behavioral and dietary factors. The combination of obesity and hypertension has two important consequences. Firstly, this combination is particularly insidious in that the populations with obesity and hypertension have high morbidity and mortality from CVD,

including coronary heart disease, congestive heart failure, sudden cardiac death, chronic kidney disease (CKD), end-stage renal disease and stroke. [85]Secondly, obesity increases the risk of treatment-resistant arterial hypertension, which therefore requires multiple medications and device therapy, such as renal sympathetic denervation. [52, 57]

- Hypertension to obesity can occur via multiple mechanisms: insulin resistance, adipokine alterations, inappropriate SNS and RAAS activation, structural and functional abnormalities in the kidney, heart and vasculature, and maladaptive immunity.
- Hyperuricaemia associated with a high-fructose diet also contributes to vascular dysfunction, renal injury and immune activation. DPP-4mediated incretin signaling can affect vascular function, immune responses and natriuresis in obesity states.
- Adipokine alterations, insulin resistance, sympathetic nervous system and renin–angiotensin aldosterone system activation, obstructive sleep apnoea, renal abnormalities, maladaptive immunity and gut microbiome changes all link hypertension to obesity.
- Hyperuricaemia associated with a high-fructose diet is emerging as a key factor in the development of hypertension associated with diet-induced obesity.
- Dysregulation of the dipeptidyl peptidase 4–incretin system contributes to the development of maladaptive immunity and associated hypertension in obesity.
- Estrogen-mediated CVD protection is compromised in individuals with obesity, thereby underscoring the greater CVD risks associated with obesity in premenopausal women compared with those in age-matched men with obesity.
- Adjunctive therapy with mineralocorticoid receptor antagonists and renal denervation is emerging as an additional therapeutic measure for management of obesity-related hypertension. [60,61,53]
- Selective leptin resistance helps explain how high levels of circulating leptin in obesity may contribute to hypertension and sympathetic overdrive despite resistance to metabolic effects of this hormone. Long-term renal sympathetic stimulation caused by high leptin levels could raise renal sympathetic tone leading to hypertension, whereas loss of leptin'sability to decrease food intake and increase thermogenesis promotes obesity by increasing adiposity.

FIG. 3 RELATIONSHIP BETWEEN HYPERTENSION AND OBESITY



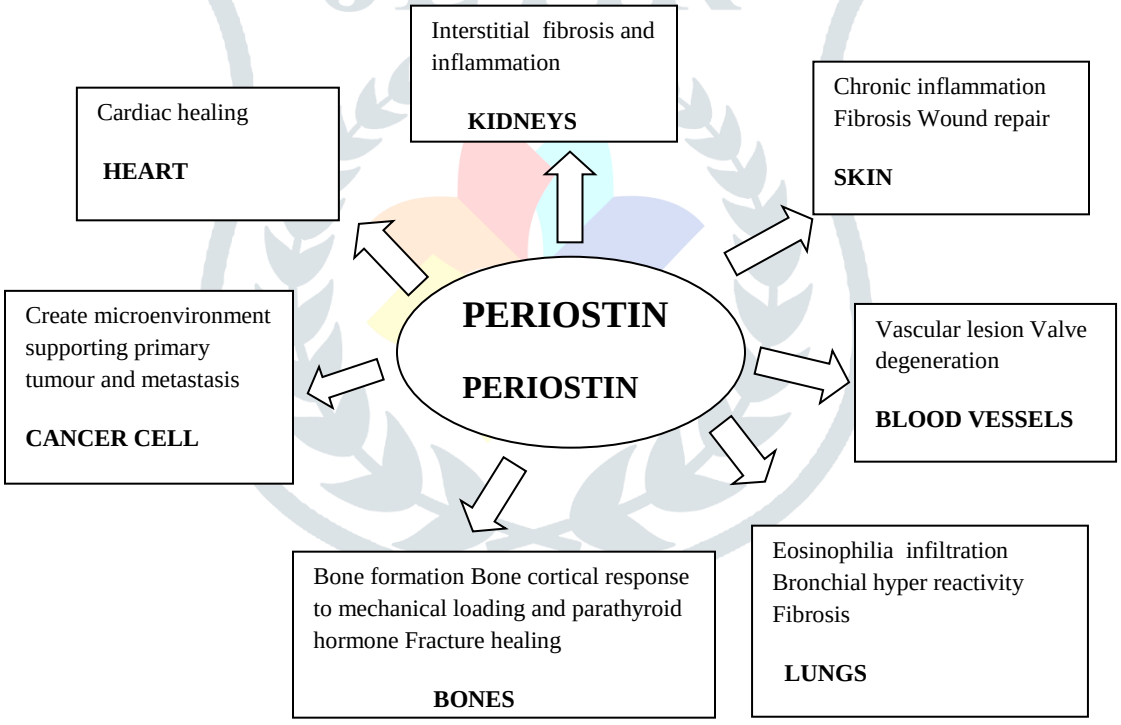
Leptin plays an important role in regulating appetite and energy homeostasis via its actions on the hypothalamus. [90,97,99] Circulating leptin concentrations are influenced by sex hormones, inflammatory cytokines and lipopolysaccharides. In vitro work has shown anabolic bone responses to the direct actions of leptin on bone cells. [53, 53]

Cardio protective nutrients: The undesirable dietary changes in the USA during the past 50 years might be further exacerbated by the imbalance in consumption of omega-6 and omega-3 fatty acids. Omega-3 fatty acids must be obtained from an individual's diet. Humans evolved on diets that contained fairly equal amounts of omega-6 and omega-3 fatty acids. However, in the past 50 years the US diet has become deficient in omega-3 fatty acid (ratio of omega-6 to omega-3 ~15:1) owing to increased consumption of plant-derived oils (soybean and corn oils) and red meat from grain-fed animals, which are rich in omega-6 but not omega-3 fatty acids. Consequently, cold water marine fish have received much attention by dieticians due to their high content of omega-3 and more balanced ratio of omega-6 to omega-3 fatty acids. In meta- analyses, fish oil supplements lower blood pressure in patients with hyper tension. However, the reports that fish oils can prevent CVD in general are inconclusive.Combination diets, notably the Dietary Approaches to Stop Hypertension (DASH) diet,which is rich in nutrients from fruits, vegetables and has modest levels of sodium, omega-3 and omega-6 fatty acids, have emerged as part of a balanced strategy for the management of hyper tension. Approaches such as the DASH diet

include green leafy (for example, cabbages, spinach and lettuces) and root (carrots and beets) vegetables that are rich in inorganic nitrate. [93] Beetroot juice, which also contains high levels of inorganic nitrate, can also lower blood pressure. [7 ,8] the nitrate content of these foods is likely to contribute to increased nitric oxide (NO) bioavailability, which has multiple beneficial pleiotropic effects in the vasculature such as vasodilation. [62] Potential mechanisms linking obesity to hypertension include dietary factors, metabolic, endothelial and vascular dysfunction, neuroendocrine imbalances, sodium retention, glomerular hyper filtration, proteinuria, and maladaptive immune and inflammatory responses.

PERIOSTIN

FIG. 4 ROLE OF PERIOSTIN IN BODY



Periostin, a matricellular protein preferentially localized in the periostealtissue,sphingosine 1-phosphate,alipidmediatorwhichactsmainlyonosteoclastogenesis and the osteocyte factors such as sclerostin.[63]

Periostin (Postn) is a 90kD extracellular matrix protein of 836 aa (in humans), originally named osteoblast specific factor 2 (OSF-2) when it was first cloned from a cDNA library prepared from the mouse osteoblastic cell line MC3T3-E1. Although the current denomination derives from its

expression in the periosteum of long bones, periostin is broadly expressed, with highest levels in the aorta, stomach, lower gastrointestinal tract, placenta, uterus, thyroid tissue and breast. It is particularly expressed during ontogenesis and in adult connective tissues submitted to mechanical stimulation (stretch), such as heart valves, skin, periodontal ligaments, tendons and bones. In bone, Postn is transcriptionally regulated by Twist, RUNX2, and C-Fos/AP1. Its expression levels are maximal in the periosteum and osteocytes and further controlled by mechanical stimuli, hormones (PTH), growth factors (TGF-β, BMP2) and cytokines (TNF-α, IL-4, IL-13, and likely PDGF), all known to have important roles in the determination and/or regulation of bone homeostasis.[64]

Periostin is a secreted extracellular matrix protein that was originally identified in cells from the mesenchymal lineage (osteoblasts, osteoblast-derived cells, the periodontal ligament, and periosteum). It has been associated with the epithelial-mesenchymal transition in cancer and with the differentiation of mesenchyme in the developing heart.[63]

Periostin is transiently up regulatedduring cell fate changes, whether they are related to alterations in physiology or to pathological changes. It influences extracellular matrix restructuring, tissue remodeling, and the epithelial-mesenchymal transition, all of which can be related to tissue healing, development, and disease. Thus, it functions as a mediator, balancing appropriate and inappropriate responses to tissue damage.[65]

Periostin has been demonstrated to be involved in various phases of bone repair: (1) early on during inflammation and angiogenesis,(2) on the recruitment of osteoprogenitors into the callus; (3) in the early stages of osteoblast differentiation and bone formation.

The periosteum covers long bones and although in adults its metabolism is considered to be low, it plays an important for controlling the diameter of bones and thus bone strength Periostin is not only involved in regulating bone formation and BMD but also could have an effect on bone strength by regulating collagen crosslinking It increases bone formation through osteoblast differentiation, cell adhesion, Wntsignalling and collagen cross-linking. Periostin is an extracellular matrix protein expressed in bone, cartilage, ligaments, lung and other sites. It was first described in 1993 and initially named osteoblastic-specific factor 2.[65,66]

PREVIOUS STUDIES

Guerrotet al, (2017) concluded that the periostin as a previously unrecognized marker associated with disease progression and regression in hypertensive nephropathy and suggest measuring

periostin may be a sensitive tool to evaluate severity, progression and response to therapy in human kidney disease associated to hypertension.

Han wuet al, (2016) suggested that periostin may serve as a potential target for the prevention of hypertension-induced myocardial fibrosis. Hypertensive myocardial fibrosis contributing to myocardial remodeling is the pathophysiological basis of hypertension and eventually results in heart failure.

Iekushiet al, **(2007)** concluded that Ang II and mechanical stretch significantly stimulated periostin expression whereas blockade of Ang II by valsartan significantly inhibited the increase in periostin expression. The results of treatment with valsartan in an MI model especially suggest that inhibition of periostin by valsartan might contribute to the beneficial effects of valsartan on cardiac remodeling. Because an increase in periostin expression is known to occur in hearts with ischemic cardiomyopathy, hypertrophic cardiomyopathy, or dilated cardiomyopathy, the inhibition of periostin by an ARB might provide a new therapeutic strategy for heart failure.

Hai-ying et al, (2017) concluded that elevation of serum uric acid level may induce renal vasoconstriction by reduction of circulating nitic oxide and activation of the rennin angiotensin system, and thereby increasing the level of blood pressure.

The relationship of hyperuricemia with hypertension in males is significantly stronger than females. The apparently protective effect of sex might be related to estrogen level.

Jennifer S. Walsh et al, (2017) Concluded that Higher serum periostin has been associated with higher fracture risk in postmenopausal women, and the association with non-vertebral fracture seems near be stronger than serum periostin is higher at the end of growth (age 16-18) than at peak bone mass and older age. At this age it is positively correlated with IGF-1 and biochemical markers of bone turnover, and negatively correlated with cortical thickness and density, suggesting a role in IGF-1 driven bone modeling and cortical consolidation.

Masanari Kuwabara et al, (2016) concluded that the serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics. Based on these facts, it is believed that the uric acid level only partly reflects the lifestyle origins of the disease, and it merely serves as a marker of cardiovascular disease. Serum uric acid levels >5 mg/dl had a higher prevalence of systolic and diastolic hypertension compared to those with levels <5 mg/ dl.

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