CHAPTER

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The Challenges of Hypertension in Obese Subjects - Indian Perspective

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The relationship between obesity and hypertension is said to be a two way street.[1] Obesity is being recognized as one of the most important risk factors for the development of hypertension.[1] Several epidemiological studies show that the age-adjusted prevalence of hypertension increases directly with body-mass-index (BMI).[1] The link between BMI and Blood Pressure (BP) appears to be stronger for systolic than diastolic BP. Central obesity, so common in Indians is much more clearly related to cardiovascular (C.V.) and metabolic risk factors than lower body obesity. Risk of developing hypertension is strongly related to both waist circumstances and waist hip ratio. The incidence of hypertension is higher in people with high waist and small hip circumference.[1] Significant proportion of USA citizens with abdominal obesity (21%-27% in males and 37-57% in females) have hypertension and 85% of hypertension occurs in subjects with BMI $\geq$ 25 kg/m^2 in Finland.[1] In our country also many hypertensives are either overweight or obese. The Nurses Health Study[2] had shown that women who lost 5 kg had significantly lower risk of developing hypertension than those who did not. Women who gained more than 25 kg after follow-up of 18 years had a five fold increase in risk of hypertension than those whose weight remained stable. Framinghum study[3] and other[4] studies have shown that future weight gain is significantly greater in hypertensive subjects than normotensives. Thus even a normal weight hypertensive is more prone to develop obesity than normotensive. This may be attributed to individual susceptibility for both hypertension and obesity or common environmental factors.[1]

Inspite of the above facts, current guidelines for hypertension-management do not provide specific recommendations for managing obese hypertensives- hence this review article.

The Indian Hypertension guideline 2007 (IHG-2007)[5] the JNC-7 (2006)[6] and British Hypertension Society guidelines (BHS IV-2004)[7] have all considered obesity (BMI $>$ 30 or increased waist hip ratio) as an independent CV-risk factor in hypertensives, besides dyslipidemia, IGT, insulin-resistance and hyperinsulinemia[6]

Management of obesity related hypertension should therefore address not only central obesity (waist circumferences $\geq$ 90 cm in Indian males and $\geq$ 80 cm in Indian females or BMI $\geq$ 25 kg/m^2)[8] and the level of hypertension but also smoking, physical inactivity, dyslipidemia, diabetes mellitus, microalbuminuria, estimated GFR less than 60 ml/min, age above 55 years in males and 65 yrs in females, and family history of coronary artery disease or stroke (in men $<$ 55 years and in females $<$ 65 years)[6].

IHG 2007[5] and JNC-7 (2003)[6], and BHS-IV. 2004[7] have accorded the first priority to weight reduction in the list of life style modification. Reducing body weight by 10 kg, lowers the systolic BP by 5-20 mm Hg[5] or 5-10 m Hg[6]. It has been calculated that maintaining ideal B.M.I (20-25 kg/m^2) alone can reduce systolic BP by 8-14 mm Hg.[5,6,7]

BP- measurement in obese hypertensive

This poses special problem. BP recorded by standard adult cuff with bladder size (12 x 26 cm) will give a spuriously high figure of BP (Pseudohypertension). BHS-IV recommends that large adult cuff with bladder size 12 x 40 cm should be used for correct recording of BP in obese hypertensives. IHG-2007[5] recommends that the bladder of the cuff should encircle and cover two thirds of the girth and length of the arm-respectively.

How does obese hypertensive differ from lean hypertensive ?

An obese hypertensive has greater risk than lean hypertensive, of developing athero-thrombotic and proinflammatory abnormalities like CAD, insulin resistance, hyperinsulinemia, glucose intolerance, increase in small dense LDL, low HDL, left ventricular hypertrophy, obesity-cardiomyopathy, raised plasminogen activator inihibitor-1 (PAI-1), high plasma fibrinogen level, reduced plasma teststerone in males, chronic inflammatory state [raised IL-6, raised C-Reactive Protein (CRP)] and endothelial dysfunction and high mortalit.[8,9,10,11,12,13,14,15,16,17,18,19,27]

An obese hypertensive has greater propensity than a non obese hypertensive to develop non-metabolic consequences.[10,11,16,17,20,26,27] These are osteoarthritis, gout, reflux esophagitis, sleep apnea syndrome, gall stone, cnacer of endometrium, breast, ovaries and biliary tract in females and cancer of prostate, colon and rectum in males. Obese hypertensives are more liable to stress-incontinence. Das[21] has suggested that hypertension is a low grade inflammatory condition.[21] Elevated plasma IL-6 and CRP in hypertensives supports this hypothesis.[21] A direct relationship between plasma CRP levels and BMI, systolic BP, HDL, smoking and hormone replacement therapy has been reported.[21,22,23] These observations suggested that the low-grade systemic inflammation occurs in people with high BMI. So in obese hypertensives, the chronic inflammatory processes are hyperactive than in lean hypertensives. Adiponectin[24] expressed exclusively in adipose tissue[25] is an anti-inflammatory, anti-diabetic and anti-athero-genic hormone. Serum adiponectin is low in young obese persons, hence their intrinsic anti-inflammatory mechanisms are at low ebb and pro-inflammatory processes are hyperactive[25].

Patho-physiological mechanisms linking obesity to hypertension

There are growing evidences that adipose tissue may be directly involved in the pathogenesis of hypertension in obese people[1,2,44].

Several mechanisms are implicated in development of hypertensives associated with obesity. These are:

- Over activation of renin-angiotensin system.
- Sympathetic nervous system overactivity.
- Insulin resistance leading to volume expansion, sodium retention and sympathetic overactivity.
- Leptin-resistance.
- Altered coagulation factors.
- Inflammation and endothelial dysfunction.

Obesity might lead to hypertension by increasing renal sodium reabsorption, impairing pressure natriuresis and increased volume expansion. Obesity has been shown to cause focal segmental glomerulosclerosis and functional nephron loss contributing to hypertension, which in turn leads to further renal injury, thereby setting off a vicious circle[44]. Causes of sympathetic over activity in obese is not well understood but stimulation of hypothalamic-pro opiomelanocortin[1] pathway by

Table 1 : Life Style Modification (LSM)[5,6,7,26,27,30,31,32,42]

1 Diet:
- Salt 6 Gm (1 teaspoonful common salt)
- Restrict calories (Reduce 500 - 1000 Kcal from previous diet)
- Restriction of total fat and saturated fat
- Low fat dairy products, plenty of green vegetables, fresh fruits and fish

2. Aerobic exercise (for one hour daily or at least 5 days a week)
- Brisk walking, cycling or swimming

3. Stop or moderate alcohol consumption (3 ounces Whiskey or 10 ounces of Wine or 24 ounces of Beer in males and half of these in females).

4. Behaviour modification:
- Make a vow to avoid sugar, sweets, honey etc
- Replace snacks between main meals by lemon-water
- Use stairs (not elevator), park vehicle away from work place or shopping complex
- Attend to telephone in standing posture.

5. Stop smoking (remember cessation of smoking may lead to excess food intake, hence stricter compliance of 1 to 4 above)
- Nicotine replacement (Nicotine SL microtab, Nicotine chewing, gums, Nicotine patches)
- Bupropion (for highly motivated person)

6. Yoga: (Pranayams, Sawashan)[29] leads to :
- Reduction of systolic and diastolic BP
- Reduction of weight and body fat percentage
- Increase in lean body mass and HDL
- Reduction in free fatty acids and LDL
- Reduction of CV risks

hyperleptinemia may be a possible reason. Also hyperinsulinemia, insulin resistance, activation of renal afferent nerves and renal mechanoreceptors, high plasma free fatty acid and angiotensin II have been implicated.

Co-existing obstructive sleep apnoea[26,27] in obese patients cause resistant hypertension[1]. Insulin resistance in obese hypertensives is thought to increase CV risks through increased activity of Renin-Angiotensin-Aldosterone System(RAAS).[1,2,44]

Obese hypertensives have usually high cholesterol, high LDL, high triglyceride and low HDL[21] and the risk of CAD and stroke are therefore more in obese hypertensives. Obese hypertensives have increased risk of developing type 2 Diabetes, coronary artery disease, dyslipidaemia and of all cause mortality[28].

Management of the obese hypertensive

Life style modification (LSM) should be advised for all obese hypertensives and anti-obesity (Table 1) and anti-hypertensive drugs only for selected patient who qualify for them. According to IHG-2007 and JNC-7 2003, weight reduction by Dietary Approach to Stop Hypertension (DASH) with diet rich in fruits, vegetables and low fat dairy products and reduced content of saturated and total fat, sodium restriction, increased physical activty and moderation of alcohol consumption will reduce systolic BP (SBP) by 5-20 mm Hg, 8-14 mm Hg, 2-8 mm Hg, 4-9 mm Hg and 2-4 mm Hg respectively. Thus LSM alone if followed strictly will reduce SBP by 21-55 mm Hg which no drug can achieve. Out of these items, weight reduction achieves the largest reduction in BP

Table 2 : Risk Stratification[5]

Risk Factor	**Stage-1 HTN** (140-159/90-99 mmHg)	**Stage-2 HTN** (160-179/100-109 mmHg)	**Stage-3 HTN** (> 180/110 mmHg)
1. Obesity + one more risk factor	Medium risk	Medium risk	Very high risk
2. Obesity + 2 or more risk factor or TOD or diabetes mellitus	High risk	High risk	Very high risk
3. Associated clinical CCD + obesity	Very high risk	Very high risk	Very high risk

Note: TOD = Target organ damage, CCD= Clinical Cardio-vascular Disease

and hence benefits the obese hypertensives the most.

Drug Therapy

Current guidelines do not provide specific recommendations for obese hypertensives[3]. However Nerkaiewicz from Poland[1] and J Scholze et al[3] from Germany in their Hypertension-Obesity-Sibutramine Study (HOS) have offered certain suggestions and so have Aneza A et al from USA.[44] For Indian physicians institution of drug-therapy should be based on recommendations of IHG 2007.[5] BHS-IV Guidelines 2004[7] have been incorporated in IHG[5]. In the risk-stratification by IHG, obesity has been explicitly recognized as a major risk factor (Table 2). The aforesaid suggestions from Germany, USA and Poland may be relevant even in Indian-perspective.

When to start anti-hypertensive drug-therapy for obese hypertensives?

In medium risk patients[5] intensive LSM should be instituted. If goal BP is not achieved in 2-3 months, drug therapy may be started. In high risk and very high risk patient,[5] drug-treatment for hypertension, obesity and associated comorbidities should be immediately initiated.

I find it more convenient to follow the BHS-IV guideline and start antihypertensive drug for all obese hypertensives whose BP by appropriate cuff size is more than 160/100 mmHg on repeated recording two weeks apart. For therapy with anti-obesity drug of obese hypertensives, the suggestions of British National Formulary -51 March 2006[41] including National Institute of Clinical Excellence[41], Narkaiwicz[1] et al, Scholze et al[3] Aneza et al, are worth consideration even for Indian patients.

Goal-level of BP in obese hypertensives

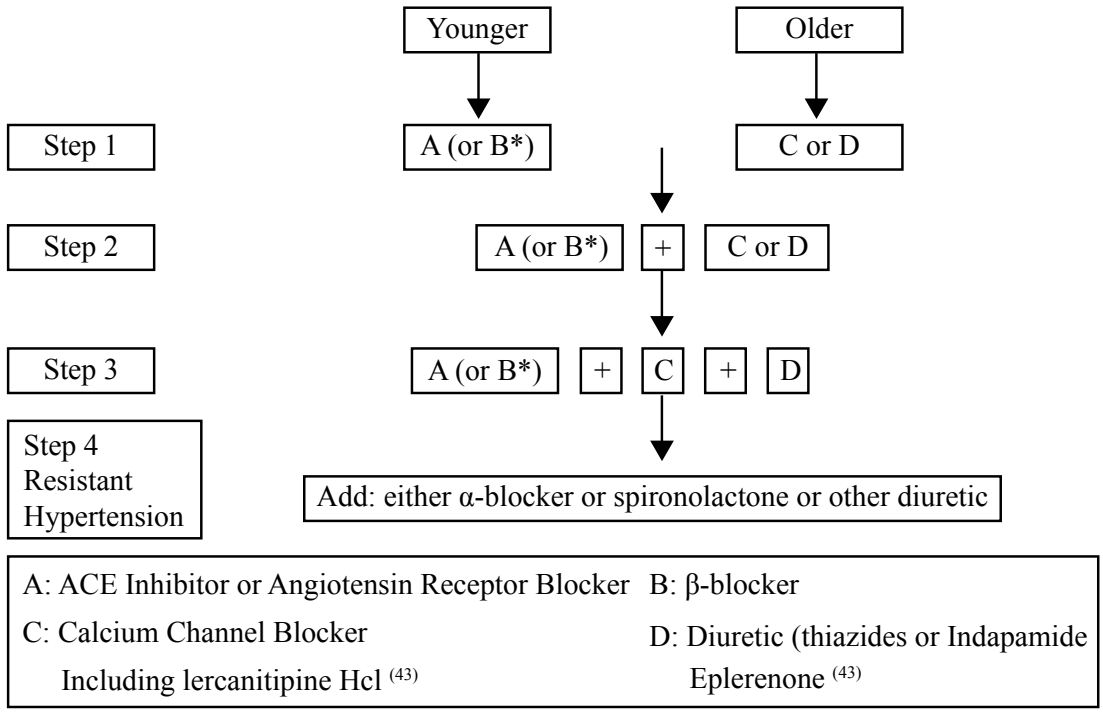
The IHG[5] recommends the goal level of BP lowering to < 120-130/80-85 mm Hg in young and middle aged and to < 140/90 mm Hg for the elderly obese hypertensives. In obesity related hypertensives with diabetes mellitus and stroke, the optimal level have been fixed as < 130/80 mmHg and < 130/85 mmHg respectively by IHG[5]. In obese patients of Type-2 diabetes or non-diabetic chronic kidney disease (CKD) and heart failure, BP should be lowered to 130/80 mm Hg or below.[5,6,7] Further benefits may accrue if BP is brought down to 125/75 mm Hg in CKD-subjects with proteinuria of 1 gm/24 hrs or more[7].

Choice of Anti-hypertensive drugs for obese -hypertensives

Ideal drug should reduce weight as well as BP. The holistic approach should address associated comorbidities like diabetes mellitus, dyslipidemia, coronary artery disease, gout, asthma, renal failure, enlarged prostate etc. Let us first consider correct anti-hypertensive drug for obese patients. Initially IHG-2007 and BHS-IV 2004, had advocated the ABCD algorithm.[5,7,43] ASCOT-BPL- trial[31] and VALUE-trial[32] Aneza et al, have sounded a warning about new onset diabetes mellitus in patients treated with β-Blockers. Taking this warning seriously BHS-IV and IHG-2007 have now modified the A(B)CD algorithm (Table 3).

Table 3 : Modified ABCD algorithm

Combinning Antihypertensive Drugs[5]



*Combination therapy involving B and D may induce more new onset diabetes compared with other combination therapies.

My belief about unsuitability of calcium channel blockers (CCB) for obese hypertensives has been potentiated by Aneza et al,[44] as these drugs may produce edema and increase the body weight. β-blockers can also increase body weight[42,44] produce dyslipidemia and impair glucose tolerance[44]. However studies of Scholze et al[3] have for the first time, suggested that combination of ACE-inhibitors and CCB has advantages compared to β-blockers - diuretic based regime. This combination (ACE-inhibitor + CCB) supports the weight reducing actions and concomitant metabolic changes induced by Sibutramine in obese hypertensives. Given the side effects of rise of BP and pulse rate by Sibutramine, this finding of Scholze needs further studies. Many studies have shown superiority of ACE-inhibitors and angiotensin-receptor blocker (ARB), as they improve insulin-sensitivity and decrease sympathetic activity compared to thiazide and β-blockers, despite similar reduction of BP.[1] But Anezia et al,[44] recommended thiazides also for obese hypertensive. LIFE-trial demonstrated greater benefit of losartan based therapy in hypertensives with LVH than atenolol. However, use of β-blockers is mandatory in obese hypertensives with angina or myocardial infarction. These conflicting observations cry for multicenteric randomized controlled trials of ARB, ACE-inhibitors and CCBs 'vis-a vis diuretic and β-blockers in Indian obese hypertensives. Till that time, it will be prudent to use ACE-inhibitors and ARBs in young obese hypertensives (high renin group) and diuretics and s-amlodipine in elderly obese hypertensives (low-renin group).

Choice of anti-obesity drugs

Only those anti-obesity drugs will be discussed

Table 4 : Classification of anti-obesity drugs[26,27]

Drugs acting on Gastro-intestinal System

a. Orlistat by neutralizing lipase

b. Rimonabant by blocking Connabinoid B_1 (CB_1) receptor in G.I.T.

Drugs acting on CNS

a. Acting via serotoninergic & nor-adrenergic pathways
   - Sibutramine
   - Fluoxetine

b. Acting via serotoninergic, nor adrenegric and dopaminergic pathways
   - Bupropion

c. Acting only via serotoninergic pathway
   - Dexfenfluramine, Fenfluramine

d. Acting via noradrenergic pathway
   - Phentermine
   - Diethylpropion } no longer used due to side effects
   - Phendimetrazine

modulating neurotransmitters

- Selective serotonin re-uptake inhibitor
  - Fluoxetine, sertraline
- CB_1 - receptor antagonist
  - Rimonabant

Anti-epileptics & anti-diabetic

- Topiramate
- Mazindol
- Zonisamide[44]
- Metformin

Recombinant human leptin

- **Dietary Supplement:** Chitosun, Ephedrine + Caffeine

Statins : (author's experience is that they reduce some weight in obese dyslipidemic patients)

which are available in India and have been permitted for human use. Experimental drugs or drugs which have been discarded due to their side effects do not come under the purview of this article. But a classification of anti-obesity drugs may be possibly referred here[26] (Table 4). It must be emphasised that anti-obesity drugs are near adjuncts to LSM. These drugs should be started in those obese hypertensives who fail to achieve a realistic weight loss inspite of 12 weeks of supervised LSM[41], and whose BMI is > 27 kg/m^2. Drugs should be discarded if weight-loss is less than 5% in first 12 weeks or weight regain occurs[41].

Combination of anti obesity drugs are contra-indicated. Continuation of anti obesity drugs beyond 2 years should be under strict medical supervision as most studies on these drugs have been carried out for 2 years only.

Out of the above drugs (Table 4) Orlistat, Rimonabant, Sibutramine, Topiramate and Zonisamide[44] can be used in obese hypertensives[44]. A randomized controlled trial conducted with zonisamide (an anti epileptic with dose dependent biphasic dopaminergic and serotoninergic activity) resulted in significantly greater weight loss and reduction of BP compared to LSM alone[44]. This drug is not available in India.

Sibutramine

It raises pulse rate and BP and many clinicians including Aneza et al and author of this article object to its use in obese hypertensives. But Scholze et al[3] in HOS-study[3] used Sibutramine in combination with ACE-inhibitors and CCB to reduce weight of obese hypertensive with good result.

Rimonabant

It may prove to be the drug of first choice for treatment of obesity in hypertensive patients as it addresses the underlying mechanisms of both obesity hypertension and cardio metabolic risks.

Mode of action: Endogenous cannabinoid Anandamide stimulates the cannabinoid-1 receptors (CB_1)[33,34,35] which are present in brain, adipose tissue, muscles, liver and gastrointestinal tract. Anandamide thereby stimulates appetite and increases visceral fat, insulin resistance and lipogenesis[33] Rimonabant, by blocking these actions of anandamide on CB_1-receptors, produces loss of weight and other beneficial effects shown in Table-5. Three multinational trials viz RIO-Europe[34], RIO-Lipid[39] RIO-North America[40], besides other

Table 5 : Actions of Rimonabant [35,36,37,38,39,40,41,42]

Site of action	Mechanisms	Effects
1. Hypothalamus	↓Food intake	Weight loss
Nucleus accumbus		Reduced Waist Circumferences
2. Adipose tissue	↑Adiponectin	Reduced Visceral fat
	↓Lipogenesis	↑HDL
	↓C Reactive Protein	↓Triglyceride
		↑Large dense particles of LDL
		↑Insulin sensitivity
3. Muscle	↑Glucose uptake	↑Insulin sensitivity
	↑O_2 - Consumption	↓Blood Sugar HbA_{1C}
4. Liver	↓Lipogenesis	Improved lipidaemia
		↑Insulin sensitivity
5. G.I. Tract	↓Satiety	weight loss
6. BP: Systolic BP	*	Reduction } (34,40)
Diastolic BP	*	Reduction } (34,40)

studies[35,36,37,38] have shown beneficial effects on obesity and hypertension.

Dose, side effects and contra-indications of Rimonabant[28,33,34,35,36,37,38,39,40] Dose 20 mg orally OD. Side effects: mood changes, nausea, diarrhoea, dizziness, upper respiratory tract infections.

Contra-indications: Pregnancy, breast feeding, affective disorders, severe renal and hepatic dysfunction and epilepsy.

Orlistat

It inhibits gastric and pancreatic lipases and thereby cause excretion of dietary fat in stool. These result in reduction of adiposity, blood cholesterol and triglyceride[28]. As it leads to fat malabsorption, it may cause deficiency of fat soluble vitamins (Vitamins A, D, E and K)[28,41] These vitamins must be supplemented. As patients experiance fatty loose stools, flatulence and fecal incontinence with the drug, they learn to avoid fatty food and fried food which are usually heavily salted. This avoidance reduces body weight and BP.

No interaction occurs with any anti-hypertensive drug and it has no negative effect on the CV-risk profile. So this drug can safely be prescribed for obese hypertensive[41,44] Advocated dose is 120 mg. orally immediately before or up to one hour after main meals to a maximum of 360 mg/day.[41] If a meal is missed or contains no fat, the dose of orlistat should be omitted.[41,44]

Summary

Obesity is the most common modifiable risk factor for hypertension[42,44] and adds to metabolic and CV risks. Anti obesity drugs should only be prescribed if supervised LSM fails. The original BHS - IV ABCD - algorithm[7,43] has been modified the light of ASCOT and VALVE trials. Modified A(B)CD algorithm should be followed in medium, high or very high risk obese hypertensives. ACE - inhibitors, ARBs and rarely thiazides may be used in obese hypertensives in combination with rimonabant, and orlistat.[44] The status of sibutramine and CCB for obese hypertensive needs further evaluation.[44]

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